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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

SOME FUNCTIONS OF THE HYPOTHALAMUS

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I appreciate the honor of appearing before you as a Harvey Lecturer, but I know that this honor comes to me, not as an individual, but as the representative of a group. The work which I shall report has been done in large part by my associates, Drs. Magoun and Fisher, and by former associates, Drs. Ingram and Kabat.

The hypothalamus is that small division of the brain which surrounds the lower part of the third ventricle. It lies at or very near the center of the head, immediately behind the optic chiasma and above the hypophysis with which it is connected by the infundibulum.

Damage to the hypothalamus, such as is caused by tumors restricted to this part of the brain, produces quite characteristic symptoms which may appear in varying combinations. The syndrome includes adiposity, polyuria, subnormal temperature, somnolence and sometimes emotional disturbances. In order to understand these symptoms it has been necessary to investigate the normal physiology of the hypothalamus and also to inquire what part, if any, the hypophysis takes in their production.

It has been claimed and quite generally believed that venous blood from the hypophysis is carried through a special system of portal veins into the capillaries of the hypothalamus and that in this way hypophyseal hormones

can act directly and selectively on the hypothalamus.[1,2] This idea has recently been shown to be false. Wislocki and King[3] have found that the blood from the hypophysis is drained through ordinary veins and that there is nothing more than a capillary anastomosis between the vessels of the hypophysis and those of the hypothalamus.

Another way by which hypophyseal hormones could reach the hypothalamus would be by direct transmissions into the cavity of the third ventricle.[4,5] Cushing[6] believes that from the ventricular fluid this hormone may penetrate to and stimulate parasympathetic centers in the hypothalamus, but the evidence for all this is rather indirect. On the other hand, as will be shown later in connection with the discussion of diabetes insipidus, it has been demonstrated that the function of the posterior lobe is subject to the control of nervous impulses reaching it from the hypothalamus by way of the supraoptico-hypophyseal tract.

Because of the nervous and possible hormonal connections between hypothalamus and hypophysis it has come to be generally believed that these two structures are associated in function. The close topographic relation between the two and the resulting difficulty in making lesions in one without involving the other has made it difficult to separate sharply the functions of each. Moreover, tumors in the one are likely to press on or invade the other, so that tumors of the hypophysis are likely to produce hypothalamic symptoms and vice versa. For this reason it has been extremely difficult to determine which functions are purely hypothalamic, which are purely hypophyseal and which are to be assigned to a complex hypothalamico-hypophyseal mechanism.

A good illustration of this difficulty is furnished by the adiposogenital syndrone frequently produced by tumors involving the structures under discussion. Shall this be attributed to a disorder of the hypothalamus, of the hypophysis or of a complex hypothalamico-hypophyseal system?[6,7] Dr. Philip Smith[8] has shown that removal of the main body of the hypophysis by the parapharyngeal ap-

proach, leaving the infundibulum and pars tuberalis in place and not injuring the hypothalamus, causes atrophy and loss of function of the genital glands without adiposity. On the other hand, injection of chromic acid into the hypophysis by the temporal approach resulted in adiposity associated with genital dystrophy. Transplantation of anterior pituitaries into hypophysectomized males caused structural and functional restoration of the testes. These experiments show conclusively that the genital dystrophy is due to deficiency of the anterior part of the hypophysis. Smith thought that the adiposity was probably due to associated injury to the hypothalamus but this conclusion is not binding because no report was made of the extent and location of such hypothalamic injury and because the possibility was not excluded that the chromic acid may have caused some dysfunction of the pars tuberalis or of the often very considerable remnants of the anterior lobe.

Diabetes Insipidus

Diabetes insipidus has furnished as perplexing a problem as has adiposogenital dystrophy, since it has developed in some cases as a result of tumors confined to the hypophysis and in other cases as a result of tumors confined to the hypothalamus, and since it can be produced in animals by properly located lesions in either of these two structures. This problem now appears to have been solved. There is good evidence that the flow of water through the kidney is held in check by an antidiuretic hormone secreted by the posterior lobe of the hypophysis which is under nervous control exerted by the hypothalamus. The antidiuretic function of this hypothalamico-hypophyseal system is lost as a result of properly placed lesions in either the hypothalamus or the hypophysis.[9, 10, 11, 12, 13]

The hypothalamus is situated below the level of the thalamus in the lateral wall and floor of the third ventricle and it extends from the posterior border of the optic chiasma backward to include the tuber cinereum and mammillary bodies. From the tuber the infundibulum extends downward to the pars nervosa or posterior part of the hypo-

physis. This develops as an outgrowth from the brain and is composed of unmyelinated nerve fibers and of modified neurological cells known as pituicytes.[14] The anterior part develops from the pharyngeal epithelium and has a glandular structure.

The photograph shown in Fig. 1 illustrates the close topographic relation of the hypothalamus and hypophysis in the cat. In the past, investigators have been hampered by the difficulty of producing lesions in either of these structures without damaging the other. It is impossible to remove the entire hypophysis including its pars tuberalis without damaging the hypothalamus, or to reach the hypothalamus by the subtemporal approach without stretching the hypophyseal stalk with the possibility of damaging the blood and nerve supply of the hypophysis.

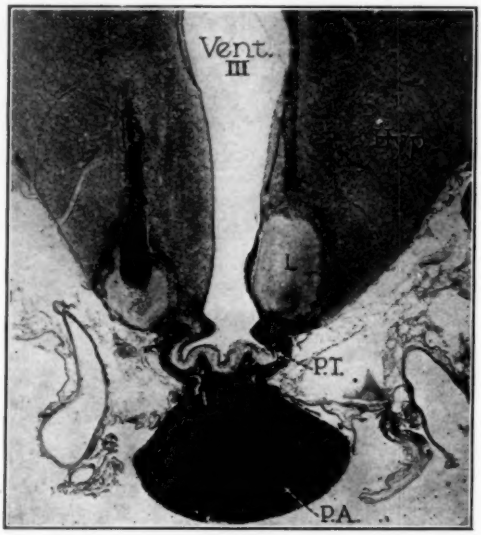

Fig. 1. Frontal section through the hypothalamus and hypophysis in the cat. Hyp, hypothalamus; L, electrolytic lesion; PA, pars anterior of hypophysis; PT, pars tuberalis of hypophysis; Vent. III, third ventricle.

We have been able to get around this difficulty by using the Horsley-Clarke stereotaxic instrument. With this instrument it is possible to insert from above, through the cerebral hemisphere and thalamus, a fine electrode, insulated except at its tip, and to make accurately placed electrolytic lesions in the hypothalamus without disturbing the infundibulum or hypophysis.

A diagrammatic representation of a mid-sagittal section through the hypothalamico-hypophyseal region of the cat is shown in Fig. 2. The ventricular cavity is continued through the stalk into the posterior lobe of the hypophysis. The pars intermedia surrounds the pars nervosa and with it forms the posterior lobe which is separated from the pars anterior by the interglandular cleft. The pars tuberalis surrounds the stalk and rests against the under surface of the hypothalamus. Nerve fibers enter the pars nervosa from the hypothalamus. These are grouped in two bundles, the larger of which is known as the supraoptico-hypophyseal tract. It arises chiefly from the supraoptic nucleus and courses near the ventral surface of the tuber through the ventral wall of the stalk into the pars nervosa. Bilateral lesions so placed in the hypothalamus as to interrupt this tract on both sides of the brain regularly cause diabetes inspidus. Subsequent microscopic examination of

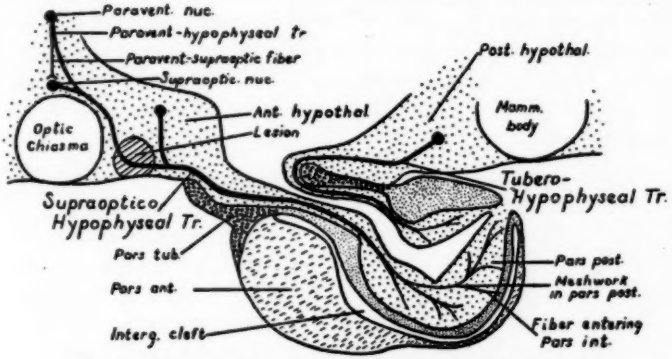

Fig. 2. Diagram of a median sagittal section through the hypothalamus and hypophysis. *Reproduced from the Anatomical Record*

the brain shows degeneration of the tract, atrophy of the supraoptic nucleus and atrophy of pars nervosa of the hypophysis. Lesions behind the infundibulum destroying the tubero-hypophyseal tract do not cause diabetes insipidus, nor do lesions still farther back in the mammillary bodies.

In silver stained longitudinal sections of the infundibular stem from the normal animal, the supraoptico-hypophyseal tract forms a conspicuous strand, but in experimental diabetes insipidus the tract almost completely degenerates. The normal pars nervosa contains a dense meshwork of unmyelinated fibers which reach it from the hypothalamus. In an atrophic pars nervosa of an animal with diabetes insipidus a few nerve fibers derived from the tubero-hypophyseal tract persist, but the vast majority of the fibers have degenerated and disappeared as a result of the interruption of the supraoptico-hypophyseal tract.

As a result of the interruption of the supraoptico-hypophyseal tract there occurs also an atrophy of the supraoptic nucleus. The atrophy involves a complete disappearance of most of the cells of the nucleus and those which remain are shrunken, and abnormal in appearance. The supraoptico-hypophyseal tract is well developed in the monkey in spite of the statements made by Mahoney and Sheehan[15] and Gagel and Mahoney.[16] When experimental diabetes insipidus is produced in this animal the tract degenerates along with its ramifications in the pars nervosa and there occurs an atrophy of the supraoptic nucleus exactly as under similar conditions in the cat.[11]

When a section of the hypophysis from a cat with diabetes insipidus is compared with a similar section from a normal cat, the pars nervosa is seen to be greatly reduced in thickness and this atrophy has resulted in an enlargement of the central cavity and of the interglandular cleft. The pars intermedia is histologically normal. In most instances it is surrounded by a ring of colloid-like material which fills the widened interglandular cleft. The significance of this colloid-like material is still unknown.

The atrophic pars nervosa contains an increased amount of connective tissue, as shown by the Van Gieson stain and a marked increase in the number of cells as seen in cresyl violet preparations. The large branching cells or pituicytes, characteristic of the normal pars nervosa, disappear. Their place is taken by a large number of cells of a different but undetermined type, causing a marked increase in cellularity.

Investigation of the development and course of the polyuria and polydipsia has brought to light a number of interesting facts. Fig. 3 shows the urine output and fluid intake in a typical case of diabetes insipidus in the cat.

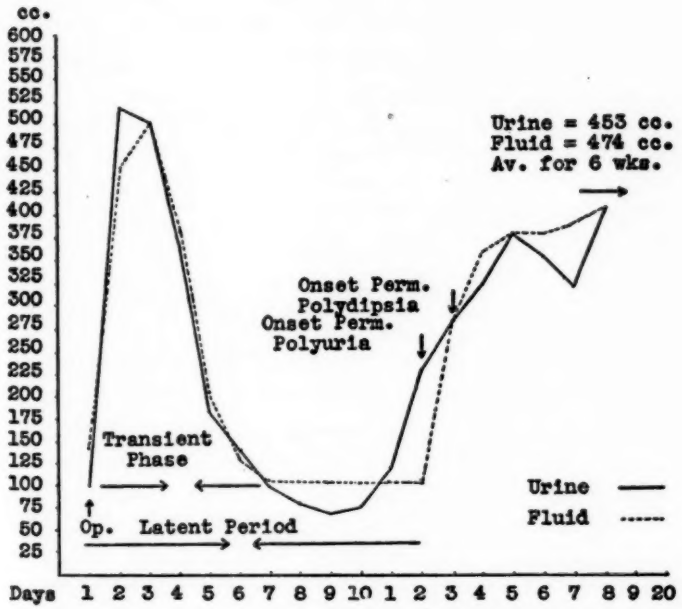

Fig. 3. Graphic representation of the course of the polyuria and polydipsia in a typical case of experimental diabetes insipidus in the cat. *Reproduced from the Anatomical Record.*

There are two phases, one transient and the other permanent. The transient phase is indicated by the first hump in the graph. On the day after the operation the urine output and fluid intake begin to increase and may reach 500 c.c. or more. After 4 or 5 days the water exchange returns to normal where it remains for about a week. Then around the 12th day, in the great majority of cases, the onset of the permanent phase is observed. It is very important to note that there is first an increase in urine output, the fluid intake lagging behind. This primacy of the polyuria is observed regularly during the onset of the permanent phase, after which the polyuria and polydipsia increase gradually and may reach a constant level within about a week. In this case the daily urine output averaged 453 c.c. for 6 weeks before the animal was killed. Once established, the disturbance persists indefinitely. We have kept a number of cats for more than 6 months and one for 9 months.

Table I gives the average daily water exchange of 8 of our cats. These were the cats which showed the most marked diabetes insipidus and the figures set down in the chart are those for the period of greatest polyuria. The daily urine outputs ranging from 543 to 939 c.c. are, therefore, the maximal results obtained. In most of the cats

TABLE I

AVERAGE DAILY

WATER EXCHANGE OF CATS WITH DIABETES INSIPIDUS DURING WEEK OF GREATEST INTENSITY

Cat. No.	*Urine Output*	*Specific Gravity*	*Fluid Intake (milk + water)*
D121	939	1.006	1166
D90	769	1.005	929
D64	673	1.008	788
D49	643	1.005	630
D9	580	1.004	708
166	591	1.005	584
D73	539	1.009	606
D102	543	1.011	566
16 normal cats	94	1.028	94

with diabetes insipidus the daily output averaged around 300 or 400 c.c. In 16 normal cats the daily output averaged 94 c.c. The low specific gravity of the urine and the high fluid intake should also be noted.

The content of pressor, oxytocic, and antidiuretic substance in three normal cat's hypophyses and in four hypophyses with atrophic posterior lobes obtained from cats with diabetes insipidus, has been determined for us by Dr. Oliver Kamm of Parke, Davis and Company. Whereas the normal glands contained 7.5, 6.0 and 5.4 pressor units respectively and 2.5, 3.5 and 2.16 oxytocic units, the glands with atrophic posterior lobes were practically inactive. A similar marked diminution was found in the antidiuretic activity. A normal gland contained 4.0 antidiuretic units, while two glands with atrophic posterior lobes contained little or none of this substance.

The results obtained from two monkeys with diabetes insipidus were similar in all essential respects to those obtained from the much larger number of cats and make it evident that the information obtained from the cats is directly applicable to primates.

It is important to remember that the permanent polyuria did not begin immediately after the lesion was placed in the hypothalamus but after a latent period of about 12 days. In the majority of the experiments a transient polyuria occurred the day after the operation but quickly subsided. We do not know what is the significance of this transient polyuria or what relationship, if any, it bears to the permanent phase. Certainly the relationship is not binding. Eight of our cats with marked diabetes insipidus failed to show the initial transient polyuria, and it was observed in only one of the two monkeys. Also, the intensity of the transient phase bears no clear relationship to the intensity of the permanent phase. We have observed animals which developed a marked permanent polyuria, although the transient phase had been slight, and others which developed slight permanents after marked transients.

Another point of interest is the relative constancy of the latent period before the onset of the permanent phase, namely, around 12 days. The latent period probably means that it takes this long for the pars nervosa to undergo degeneration or for the hormones which it contains to be absorbed.

We have had available for study 72 cats in which this disturbance in water balance has been permanent. Of these, 64 have been killed and autopsied and 8 are living in the laboratory. Diabetes insipidus was also produced in two monkeys. At this time it has been possible only to summarize briefly the results obtained. The detailed evidence has in part been published elsewhere[9, 13] and it is all being brought together for publication in monograph form.

That diabetes insipidus is a hormonal disturbance due to deficiency or absence of antidiuretic principle secreted by the posterior lobe seems evident from the constant occurrence of atrophy of the posterior lobe in our cats and monkeys and also from the small amount of antidiuretic hormone present in the atrophic glands subjected to assay, the primacy of the polyuria, and the fact that the polyuria and polydipsia can be controlled by the injection of adequate doses of pitressin.

The main objection to the acceptance of the theory that diabetes insipidus is caused by a deficient secretion of antidiuretic principle by the posterior lobe is that total hypophysectomy does not result in this disorder. This objection is beginning to lose its force because of recent experimental evidence pointing to a participation of the anterior lobe in the regulation of water metabolism. Von Hann[17] in 1918 first promulgated the theory that normal water metabolism is maintained through an antagonism between the posterior and anterior lobes of the hypophysis, because diabetes insipidus was found to occur clinically only if the posterior lobe was destroyed while the anterior lobe remained intact. Destruction of both lobes failed to cause polyuria. Richter[18] has presented evidence in favor

of the von Hann theory. He reported that total removal of the hypophysis produced a temporary polyuria in 28 rats, a permanent diabetes insipidus in none, while removal of the posterior lobe alone resulted in a permanent polyuria. He concluded that the degree of the permanent diabetes insipidus seems to depend on the amount of the anterior lobe remaining intact.

Richter's observations on the rat have been confirmed in the cat.[13] Since the infundibular stem is composed of the same kind of tissue as the pars nervosa it is necessary that this should be removed along with the posterior lobe. It was found that permanent polyuria followed such removal in the cat providing the anterior lobe was left relatively intact.

That the same factors are involved in the production of diabetes insipidus in man is shown by recent observations of Biggart[19] who this year reported two cases in both of which there was involvement of the supraoptic nuclei and of the posterior lobe.

Our conception of the pathological physiology of diabetes insipidus represents a combination of the von Hann theory with the view that the hypothalamus regulates the secretory activity of the pars nervosa through the supraoptico-hypophyseal system. An adequate injury to this system leads to a deficiency of the antidiuretic substance. The diminution in the amount of this hormone brings about a primary polyuria which is followed by a secondary and compensatory polydipsia. The polyuria which develops can be thought of as representing the resultant of diuretic processes in the body unchecked by an antidiuretic mechanism. These diuretic processes are normally under the control of the anterior lobe of the hypophysis and the polyuria may, therefore, be thought of as resulting from an uncompensated activity of this gland. In this sense, then, one may speak of diabetes insipidus being caused by a disturbance of the equilibrium normally obtaining between the posterior and anterior lobes of the hypophysis. The anterior lobe can be thought of as exert-

ing its diuretic influence through its general control over metabolism and activity, rather than through a specific diuretic hormone.

The Importance of the Hypothalamus for Sympathetic Activity and Emotional Expression

There are two very different channels through which the hypothalamus can exert its influence upon the body. One channel is formed by the nerve fibers running to the pars nervosa of the hypophysis and the hormone or hormones secreted by it. We have seen that this is very important in the regulation of the flow of water through the kidneys. What, if any, other influence is exerted by the hypothalamus through this channel remains to be discovered. The other channel is purely nervous and consists of connections between the hypothalamus and other parts of the nervous system. Here we need mention only the ascending connections with the cerebral cortex by way of the medial thalamic nuclei[20] and the descending connections with the somatic and visceral centers of the brain stem and spinal cord, and, through the spinal cord, with the sympathetic system. Bronk[21] has shown that the hypothalamus initiates nerve impulses which are discharged through the sympathetic nerves. Since, as we shall see, the hypothalamus is the chief center for the sympathetic system, these visceral connections are of major importance.

While isolated sympathetic responses do occur it is common for the entire sympathetic system to be thrown into action at once. Such generalized visceral activity always occurs during intense emotional excitement. During such excitement the pupils dilate, the hair bristles, the heart beats more rapidly, arterioles constrict causing a rise in blood pressure, the bronchioles dilate, and increased amounts of adrenalin and sugar are thrown into the blood stream. All of these changes are brought about through the sympathetic system and, as Cannon[22] has pointed out, they serve a useful purpose in preparing the body to

respond vigorously to the situation which evoked the emotional excitement. This unified activity of the sympathetic system, which forms such an important part of the reactions of fear and rage, is brought about by the activity of the hypothalamus.

The hypothalamus is the center for the integration of the visceral and somatic components of emotional expression. When it is removed, a fully developed emotional response is no longer possible and when it is stimulated electrically it can be made to call forth a typical rage reaction. This does not mean that rage and fear as conscious emotions are associated with the activity of the hypothalamus alone. No doubt the reverberations of this activity through the thalamus and cerebral cortex are fully as important for conscious emotions. This phase of the subject has been dealt with in detail by Dr. Cannon[23] and need not detain us here. But in order to prevent misunderstanding it is necessary to emphasize at this point the fundamental distinction between emotional expression as a type of reaction and emotional experience as a phase of consciousness. Dealing with animals we can, of course, study only reactions.

Bard[24, 25] was able to show that if all of the brain above the hypothalamus was cut away, the cat thus deprived of its cerebral hemispheres was more irritable than a normal animal and when restrained on an animal board responded to slight stimulation by struggling, clawing, lashing of the tail, a snarling expression, rapid deep respiration and, in addition, signs of wide-spread sympathetic activity, erection of hair, sweating, increased blood pressure and heart rate, and sometimes dilatation of the pupils. Since it was reasonable to suppose that the removal of the cerebral cortex had eliminated any possibility of conscious anger, this reaction-complex was called sham rage. When Bard removed the hypothalamus along with all of the brain in front of it, sham rage could no longer be elicited. From these results the conclusion was justified that the nervous impulses which evoke the rage reaction have their origin in the hypothalamus.

Cats from which all of the brain above the hypothalamus was removed by Dr. Hinsey[26] were left free from restraint. Instead of the sham rage exhibited by Bard's cats they showed alternating periods of activity and repose. After lying quietly for 5 or 10 minutes they would get on their feet and walk restlessly about for a few minutes and then rest again. Restlessness which in these unrestrained animals expended itself in walking vented itself in fits of sham rage in Bard's animals tied to a board.

Confirmation of the conclusions reached by Bard have been obtained by electrical stimulation of the hypothalamus.[27, 28, 29, 30, 31] In cats under ether anesthesia a bipolar needle electrode was inserted into the brain so that the bare tips of the constituent wires were in the hypothalamus and the electrode was then immovably fixed to the skull. After the animal had recovered from the anesthesia and was resting quietly, a faradic stimulus near threshold strength was applied through the buried electrode. At the onset of stimulation the animal became alert, raising its head and opening its eyes, disclosing dilated pupils. The respiration increased in rate and depth and the animal soon began to struggle, clawing, biting and trying to free itself from the hammock in which it was restrained. If the stimulus was continued the hair on the back and tail began to bristle, sweat appeared on the pads of the feet and saliva ran from the mouth. When such an animal was given a barium meal and examined under a fluoroscope it was seen that stimulation of the hypothalamus caused an immediate cessation of gastro-intestinal peristalsis due to inhibition of the gut through the sympathetic system. In all these respects the cats behaved as they would had they been threatened by a barking dog.

The reactions were specifically hypothalamic in origin. Except when very strong stimuli were used, which spread to the hypothalamus, similar reactions could not be elicited from surrounding parts of the brain such as the thalamus, internal capsule, septum, and infundibular stalk.

Sometimes the stimulation caused evacuation of the bladder, a parasympathetic response, but aside from this the only visceral reactions observed were elicited through the intermediation of the sympathetic system. Irrespective of the location of the electrode in the hypothalamus and even when the electrode was in the region of the anterior commissure or near the infundibulum, stimulation never activated the vagus so as to cause an augmentation of peristalsis. No effect upon the gut was obtained until the strength of current was sufficient to stop gastro-intestinal motility.

These observations were made on unanesthetized cats without graphic recording. In another series of experiments, carried out under light nembutal anesthesia, kymographic records were obtained showing the rise in blood pressure, increased intravesical tension and augmentation of respiration which result from hypothalamic stimulation. In both series of experiments the Horsley-Clarke stereotaxic instrument was used to insert the electrode from above downward through the cerebral hemisphere and thalamus to the desired point in the hypothalamus. This instrument is so designed that, when it is anchored to the cat's head and properly oriented with reference to it by clamps on the lower margins of the orbits and plugs in the external auditory meatuses, it is possible to insert an electrode into the brain from above or from behind in such a manner that its tip will be in contact with any chosen nucleus or fiber tract whose coordinates have previously been ascertained in terms of three rectilinear coordinates with reference to a fixed zero point in the interior of the brain.

In cats under light nembutal anesthesia the hypothalamus and surrounding territory were systematically explored by stimulating in orderly succession every cubic millimeter of their substance. A record was kept giving the coordinates of each point stimulated and the nature of the response. The exact location of each point stimulated was later checked by microscopical study of the brain. For

stimulation we used a faradic current slightly above threshold strength. The bipolar electrode was not more than 0.9 mm. in diameter, and the bare tips of the enameled wires, of which it was composed, were separated by a short distance (about 0.2 mm.) along its long axis.

Stimulation of the hypothalamus causes vasoconstriction with resultant rise in blood pressure, augmentation in rate and depth of respiration, and increased intravesical tension due to contraction of the bladder. It also causes dilatation of the pupils. Vasoconstriction and pupillary dilatation are responses mediated through the sympathetic system. They occur in association with increased rate and depth of respiration during hypothalamic stimulation and also during intense emotional excitement. Contraction of the bladder is a parasympathetic response mediated through the visceral branches of the sacral nerves.

These autonomic and respiratory responses to hypothalamic stimulation have a short latent period. Some seconds after they have made their appearance, the excitation caused by continued hypothalamic stimulation frequently spreads to somatic motor centers causing running movements or even struggling. But it is clear that the rise in blood pressure and increased intravesical tension are not due to the contraction of skeletal muscles, because these autonomic responses appear first and are represented on the kymograph records by smooth curves. Furthermore, they can be obtained just as well in an animal in which contraction of skeletal muscles has been abolished by curara.

These visceral reactions are obtained most readily from the region occupied by the medial forebrain bundle in the lateral part of the hypothalamus, Fig. 4B. They can also be obtained from the gray matter surrounding the fornix and sometimes from the medial edge of the internal capsule, but since they cannot be obtained from these fiber bundles excepting where they border on a line within the hypothalamus, they are not due to stimulation of the fibers contained within these bundles. Qualification of this state-

ment is required so far as the medial forebrain bundle is concerned. This fiber tract arises farther forward in the brain and runs backward into the lateral part of the hypothalamus, where it appears probable that it is joined by fibers from the more medially situated hypothalamic nuclei; and the presence within it of these fibers of hypothalamic origin may be the chief reason for the reactivity of the lateral hypothalamic area. It is not possible to be certain about this because at this point anatomical and physiological evidence are in conflict.

The visceral reactions so characteristic for the hypothalamus are not obtained from the overlying thalamus. From the region immediately in front of the hypothalamus, i.e., from the region surrounding the anterior commissure, there are obtained good bladder contractions associated with a decrease in the rate and depth of respiration and sometimes also a fall in blood pressure, Fig. 4A. Because of the great regularity with which parasympathetic bladder reactions, uncomplicated by any sympathetic activity, are obtained from the region surrounding the anterior commissure and from the adjacent portion of the septum, it seems probable that nuclear masses concerned in this reaction are located here.

Occasionally we have obtained from stimulating the septum and the region around the anterior commissure a good depressor reaction with a definite slowing of the pulse indicating an inhibition of the heart through the vagus nerve. This is accompanied by an inhibition of respiration.

On the drawings in Fig. 4 have been indicated the points which, on stimulation, yielded changes in blood pressure. Triangles represent falls; large black dots, marked rises; and crosses, moderate rises of intraarterial tension. A represents a section through the anterior commissure and optic chiasma, i.e., in a plane just in front of the hypothalamus. At this level drops in blood pressure were frequently obtained from the septum and from the gray matter surrounding the anterior commissure. The grouping of large black dots just above the optic chiasma represents the

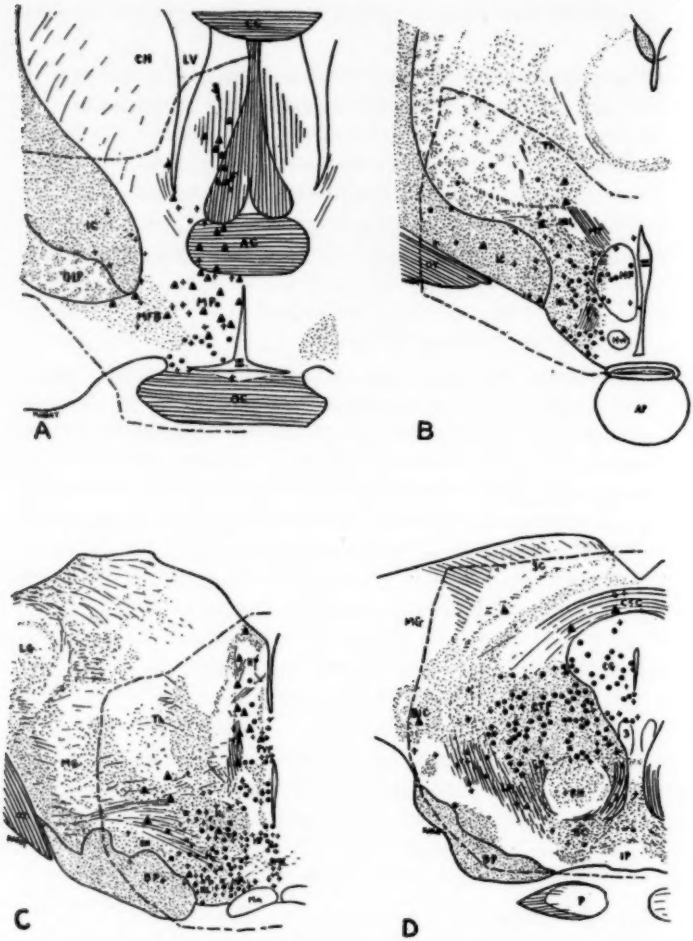

Fig. 4. Drawings from frontal sections through the brain of the cat. A, through the anterior commissure; B and C, successive levels from before backward through the thalamus and hypothalamus; D, through the mesencephalon. AC, anterior commissure; AP, anterior lobe of the pituitary; BP, basis pedunculi; CC, corpus callosum; CN, caudate nucleus; F, fornix; FR, habenulopeduncular tract; GLP, globus pallidus; H1, H2 fields of Forel; H, habenula; HL, lateral hypothalamic area; HP, nucleus hypothalamicus posterior; Hvl, nucleus hypothalamicus ventrolateralis; IC, internal capsule; LG, lateral geniculate body; LV, lateral ventricle; MFB, medial bundle of the forebrain; MG, medial geniculate body; Mm, medial mammillary nucleus; MPo, medial preoptic area; MT, mamillothalamic tract; NH1, nucleus of H1 field of Forel; OC, optic chiasm; OT, optic tract; PVF, periventricular fibers; S, septum pellucidum; SN, substantia nigra; Th, thalamus, and III, third ventricle. *Reproduced from the Archives of Neurology and Psychiatry.*

anterior end of the hypothalamic sympathetic center from which marked rises in blood pressure were obtained. B and C are successive sections from before backward through the hypothalamus and D through the mesencephalon. In each, the large black dots represent points from which marked rises in blood pressure were elicited.

On similar charts there have been plotted the points which, upon stimulation, yielded changes in the diameter of the pupils, and those points from which contraction of the bladder was obtained. A comparison of these charts suggests that the region just in front of the hypothalamus may perhaps represent a general parasympathetic center. This region includes the gray matter around the anterior commissure and near the ventral tip of the lateral ventricle and parts of the septum and preoptic area, Fig. 4A. Stimulation of this region regularly causes contraction of the bladder, sometimes also a fall in blood pressure, rarely constriction of the pupil, and very rarely indeed slowing of the heart. All of these are parasympathetic reactions, but if this is a general parasympathetic center there must be some reason why constriction of the pupil and slowing of the heart are not more frequently obtained. Stimulation of this region also causes an inhibition of respiration.

The sympathetic center in the hypothalamus yields, on stimulation, augmentation, instead of inhibition, of respiration, and also rises in blood pressure and dilatation of the pupils. From the sympathetic center there can be elicited also contraction of the bladder, but this has been interpreted as due to stimulation of fibers, arising in the center for the bladder situated farther forward and running backward through the sympathetic center to reach the spinal cord.

Near the caudal end of the hypothalamus the reactive zone includes the posterior hypothalamic nucleus and the gray matter surrounding the third ventricle, Fig. 4C. Sympathetic reactions are also obtained with great regularity behind the hypothalamus from the mesencephalic tegmentum and the central gray matter surrounding the

cerebral aqueduct, Fig. 4D. Whether the sympathetic center itself extends from the hypothalamus into the midbrain or only sends descending fibers down the brain stem, remains to be determined.

It has been generally believed that the impulses from the hypothalamus descend through the central gray matter covering the floor of the fourth ventricle. To test this assumption a cut was made across the ventricular floor. The rise in blood pressure and contraction of the bladder caused by hypothalamic stimulation were approximately the same after as before the section, showing that the pathways from the hypothalamus run elsewhere than through the ventricular floor.

In other cats bilateral cuts were made severing the lateral parts of the pons and leaving the floor of the fourth ventricle intact. The vasomotor and respiratory reactions caused by hypothalamic stimulation were greatly reduced by such lateral sections. This and other evidence indicates that the pathway from the hypothalamus descends through the pons chiefly in the lateral part of the tegmentum.[32]

In addition to its effects exerted directly through nerve fibers, stimulation of the hypothalamus results in the formation of the hormones, adrenin and sympathin which become distributed through the body in the blood stream and serve to spread, reinforce and prolong the autonomic excitation. It has been possible, by a technique which cannot here be given, to distinguish between these two hormones and to show that following hypothalamic stimulation both are present in the blood in increased amounts.[33]

Somnolence

In view of the emotional excitement and the visceral and somatic activity caused by hypothalamic stimulation it is not surprising that emotional stolidity and somnolence are caused by lesions of the hypothalamus. The making of bilateral hypothalamic lesions caused a striking change in the behavior of the normally very wild and excitable rhesus monkeys. They became drowsy or even somnolent and when awakened were tame and tractable.

These monkeys with hypothalamic lesions had a strong grasp reflex and would hang from a rod supporting their weight with their arms. The lesions which were responsible for the somnolence were bilateral and were situated in the lateral part of the hypothalamus some distance from the midline, Fig. 5. They partially destroyed the region which, on stimulation, produces the signs of emotional excitement.

Most of these monkeys recovered from the somnolence in a few days but a few remained tame and drowsy for many weeks. In some there was, in addition to the bilaterally placed lesions in the lateral hypothalamus, considerable secondary involvement of the thalamic nuclei. It is quite possible that such thalamic damage may aggravate and prolong the symptoms caused by hypothalamic lesions. But lesions confined to the thalamus have not in our experience caused somnolence. In several monkeys, which were not at all drowsy but instead remained alert and active, large lesions were found on both sides of the thalamus.

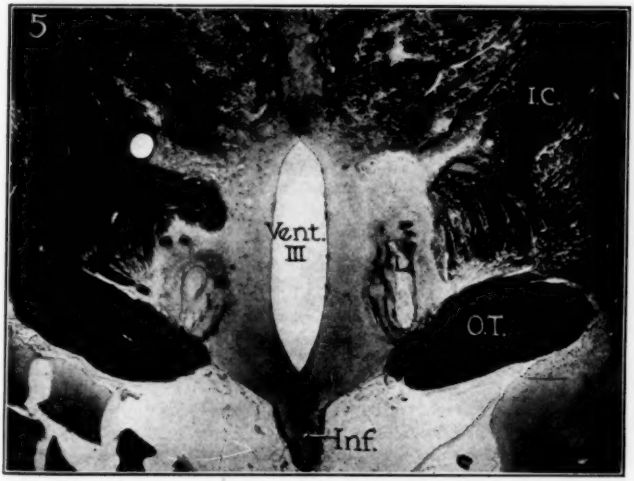

Fig. 5. Photomicrograph of a frontal section of the brain of a monkey, showing in the hypothalamus the bilateral lesions (L, L) which caused somnolence. IC, internal capsule; Inf., infundibulum, OT, optic tract; Vent. III, third ventricle.

The monkey with the very large thalamic lesions shown in Fig. 6 awakened from the anesthetic in the normal manner and thereafter showed no signs of drowsiness but remained alert and active. It was a little less afraid than before the operation but when the door of the cage was opened it would jump around in the rear of the cage, chatter and grimace. Its capacity for emotional expression was not impaired. There was some impairment of the finer movements of the hands but no other motor difficulty. The deficiency in motor initiative, which was such a conspicuous feature in somnolent monkeys, was not seen in monkeys with purely thalamic lesions. The amount of sensory disturbance could not be satisfactorily determined, because it is extremely difficult to make reliable tests of sensory function in wild monkeys.

The somnolent monkeys with hypothalamic lesions could be awakened without difficulty but would go off to

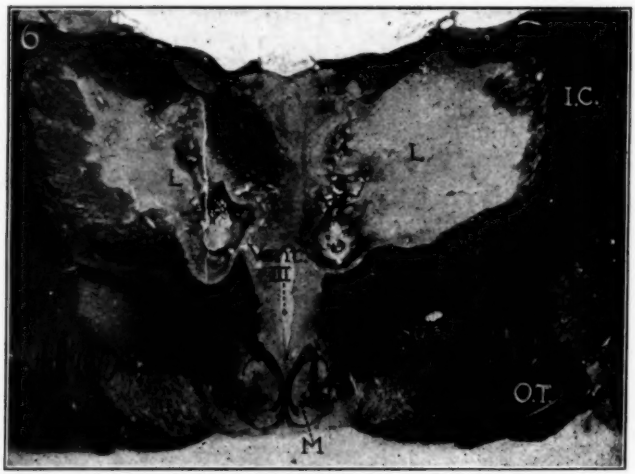

Fig. 6. Photomicrograph of a frontal section of the brain of a monkey, showing in the thalamus large bilateral lesions (L, L) which did not cause somnolence. The subthalamus and hypothalamus are intact. IC, internal capsule; M, medial mammillary nucleus; OT, optic tract; Sub., subthalamus; OT, optic tract.

sleep again as soon as they were left undisturbed. They often would fall asleep while eating and with the mouth full of food. When awakened they were emotionally unreactive. During the period of recovery, when the drowsiness had disappeared and they were again alert, they remained free from fear and allowed themselves to be handled and petted. Their faces were blank and free from wrinkles indicating relaxation of the facial muscles. This gave them a sad vacant expression. Their faces failed to register the play of emotions so characteristic of the wild monkey in captivity.

It was found easy to produce somnolence also in cats by lesions in the region of the mammillary bodies and between them and the third nerve.[34] In addition to the pronounced drowsiness these cats showed a peculiar plasticity of the body such that they would maintain odd postures into which they were molded by the experimenter. In this combination of somnolence and plasticity, they resembled patients with the cataleptic type of encephalitis lethargica and as often occurs in these patients, there was not uncommonly an involvement of the oculomotor nerve. We saw a comparable condition of plasticity in only one monkey. Perhaps this can be accounted for by a difference in the location of the lesions in the two series of experiments.

In the cats the lesions involved the caudal end of the hypothalamus and the region of transition between this and the midbrain. The location of the lesions was consistent with the assumption that the somnolence was produced by blocking the passage of impulses backward from the hypothalamus to the brain stem and spinal cord. No damage was done in front of the mammillary bodies. The rostral two-thirds or three-fourths of the hypothalamus was intact as was also its connection with the cerebral cortex through the medial group of thalamic nuclei. This would indicate that involvement of the connections between the hypothalamus and the cortex by way of the medial nuclei of the thalamus is not essential for the production of somnolence.

In both cat and monkey the medial lemniscus and other sensory pathways to the thalamus and cerebral cortex were intact, and, likewise, the great efferent pathways in the cerebral peduncles. The somnolence was not due to the interruption of connections between the cerebral hemispheres and lower lying centers of the nervous system.

It is certain that the hypothalamus is concerned in some special way with the regulation of the alternating sleep-waking rhythm. Lesions farther forward in the region of the optic chiasma or farther back in the red nuclei or higher up in the thalamus do not cause somnolence. It may seem strange that hypothalamic lesions which do not interrupt any of the great sensory pathways to the cerebral cortex should produce sleep, but the explanation seems to lie in the loss of the emotional drive normally exerted by the hypothalamus.

Somnolence is often seen in patients with tumors involving the hypothalamus.[35, 36] Furthermore, in the epidemic form of sleeping sickness, known as encephalitis lethargica, the gray matter beneath the floor of the third ventricle and in the zone of transition between this and the cerebral aqueduct, is extensively involved. Our observations are, therefore, not entirely new. It has been known for years that some part of the brain, situated in this general region, is concerned with the regulation of sleep. From these experiments on monkeys and cats we have obtained more precise information as to the part of the brain involved and have learned that the emotional drive furnished by the hypothalamus is an important factor in maintaining the waking state.

Temperature Control

It is now generally admitted that the hypothalamus serves as a thermostat regulating body temperature[35, 37, 38, 39, 40, 41, 42] but previous work has not shown clearly what part of the hypothalamus serves this function. In investigations designed to answer this question and to determine whether or not one and the same mechanism protects the animal against both overheating and excessive cooling,

electrolytic lesions were placed in the hypothalamus of young Macacus rhesus monkeys, weighing from three to six pounds, and in adult cats.[43, 44]

The animals were kept under observation for several weeks. They were free from infection and quite normal except for the disturbance in temperature regulation and other signs of hypothalamic injury such as polyuria, drowsiness and emotional stolidity. This is important because most previous observations have been made on acute preparations or on animals which lived but a few days, and which, because of the gross nature of the brain lesions, were far from normal.

Some of our animals which showed a tendency to run a subnormal temperature were kept for a time in an incubator regulated to run at 84° to 86° F., but others were kept from the start under ordinary room conditions. Rectal temperature readings were made each morning. Tests were made to determine the ability of the animals to react to room temperatures higher and lower than normal. Similar observations were made on normal cats and monkeys to obtain standards for comparison.

Some of the monkeys with hypothalamic lesions showed marked postoperative rises in temperature which returned to normal in a day or two. Those of another group were unable to keep the temperature up to the normal level. The monkeys in this second group were poikilothermic and their temperature rose and fell with that of their surroundings. But, putting aside for the moment the dual nature of the loss in the capacity for heat regulation, it will be convenient to speak of the first group as showing hyperthermia and the second hypothermia. Of the twenty-nine monkeys, eight showed transient postoperative hyperthermia, thirteen showed more or less prolonged hypothermia and eight others showed no significant deviations from the normal when kept in a moderately warm room.

The operations were performed in the morning. During the afternoon the hyperthermic monkeys showed marked postoperative rises in rectal temperature reaching 105 or

106, 4 or 5 degrees above the normal which is 101. In most instances the temperature fell to normal on the second day, but in three not until the third day. These monkeys never ran subnormal temperatures. In sharp contrast to those just described, the monkeys of the hypothermic group lost heat rapidly during the afternoon following the operation and required the application of external heat. They ran a subnormal temperature for many days and remained in surprisingly good health with rectal temperatures ranging from 90 to 95°. They did not shiver.

Monkey 39 may be taken as an example. Two days after the operation the animal was in the incubator and had a rectal temperature of 97.4°. After 1 hour exposure to a room temperature of 77° the rectal temperature fell to 95.8°. On the 10th day the animal had been out of the incubator for 24 hours at a room temperature of 75.2° and the rectal temperature was 93.2°. A day later under similar conditions it had fallen to 88.1°. The animal was put back in the incubator and its temperature rose to 98.1°. Set out again into the room, the animal continued to run a subnormal temperature for about 2 weeks more and then in warm July weather the rectal temperature rose to normal. But this recovery from hypothermia was only very partial because on the 36th day, after one hour exposure to a room temperature of 64.5°, the rectal temperature fell to 94.4°.

These hypothermic monkeys were really poikilothermic. When they were subjected to gradually increasing external temperatures beginning at 84° and increasing during a three-hour period to 102° or 103° the rectal temperature rose steadily reaching 105° or 106°. In none of the operated monkeys was sweating observed. Normal monkeys subjected to the same treatment perspired and their rectal temperature did not rise above 103°.

Microscopic study of the brains revealed a fundamental difference in the location of the lesions in the hypothermic monkeys from those in the hyperthermic ones. Those monkeys which ran subnormal temperatures had lesions

extending far back in the lateral hypothalamic area along the lateral sides of the mammillary nuclei.

In sharp contrast to the lesions just described are those found in the monkeys which developed high temperatures on the afternoon of the operation. In this group the lesions were restricted to the anterior part of the hypothalamus. They involved the region above the optic chiasma and extended backward to the level of the infundibulum or a little beyond but did not reach the mammillary region.

Defective regulation against heat was also found in cats with anterior hypothalamic lesions. When normal cats are heated and the rectal temperature is plotted on the ordinate against the rate of respiration on the abscissa it will be seen that the curve rises slowly, indicating that a small rise in rectal temperature is accompanied by a great increase in respiratory rate which may reach three hundred per minute. When cats with anterior hypothalamic lesions are treated in the same way it becomes apparent that rises in rectal temperature up to 105 or higher are associated with relatively little increase in respiratory rate.

Fig. 7 shows the location and extent of the lesion in one of these cats. The infundibulum has been destroyed by lesions, which involve the floor of the anterior part of the third ventricle and extend forward over the optic chiasma.

The cat which had the lesions shown in Fig. 7 ran a temperature definitely above normal, varying between 103° and 104° during the first four postoperative days. Thereafter, the temperature was normal. On the twelfth day the cat was subjected to a freezing temperature of 32° for three hours and its rectal temperature fell less than half a degree. In spite of the destruction of the anterior part of the hypothalamus there was, therefore, no loss in the capacity to keep the body temperature up to normal level. On the fourteenth day the cat was subjected to an external temperature of 103° and the rectal temperature rose rapidly from 100.6° to 105.3° in one and one-half hours. The cat's temperature had risen to 104° before there was much increase in respiratory rate and panting did not begin until it had reached 105.3°. There was no sweating.

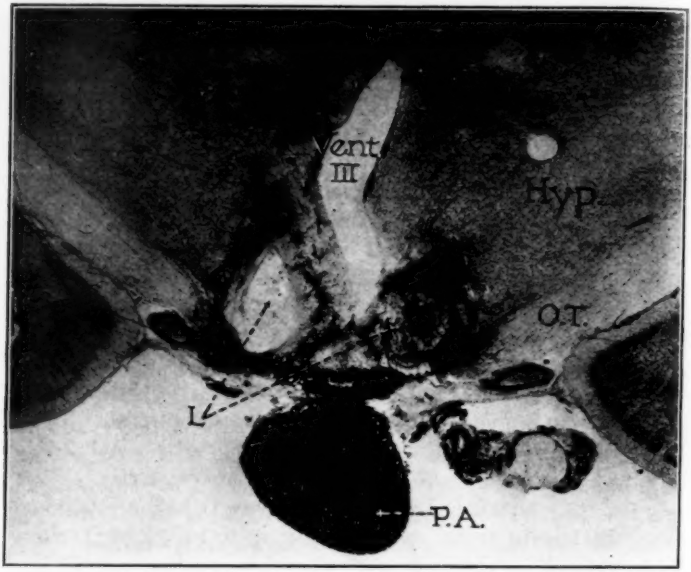

Fig. 7. Photomicrograph from a frontal section of the hypothalamus of a cat with defective regulation against heat. Hyp., hypothalamus; L, lesions; OT, optic tract; PA, pars anterior of the hypophysis; Vent. III, third ventricle.

Thirty-two cats with anterior hypothalamic lesions were subjected to this heat test. The average rectal temperature at which panting began was 105°. Eight of them failed to pant, although their temperatures were raised to 106° or higher. There was no sweating even on the pads of the feet.

Thirty-seven of these operated cats were subjected for three hours to external temperatures near the freezing point. They all shivered like normal cats. Twenty-six of them maintained their body temperatures above 100° and in only 4 did it fall below 98°. In the cats which failed to keep the body temperature quite up to normal the lesions were found to have extended farther back than usual involving the posterior hypothalamic nucleus and in some cases also the rostral part of the mammillary bodies.

These experiments on cats and monkeys confirm the now quite generally accepted view that the hypothalamus is concerned with the regulation of body temperature. Furthermore, evidence has been obtained which indicates that the anterior part of the hypothalamus, above the optic chiasma and infundibulum, is concerned with preventing abnormal rises in body temperatures and that the posterior part is concerned in preventing the body from becoming too cold.

After anterior lesions the animals often show transient postoperative hyperthermia and are unable to protect themselves against rising external temperatures but are practically normal in their reaction against cold.

After posterior lesions the animals run subnormal temperatures and are easily chilled. The data so far available seems to indicate that these animals are also unable to protect themselves against heating. They seem to be poikilothermous. Perhaps this can be explained by assuming that the descending pathway from the anterior hypothalamus, concerned with protection against overheating, is destroyed along with the mechanism which protects against cooling when the posterior part of the hypothalamus is destroyed.

Summary

In conclusion it may be said that the hypothalamus exerts its important regulatory functions through two channels. By way of the hypothalamico-hypophyseal tract it controls the rate of elimination of water through the kidneys. The interruption of this tract results in the atrophy of the pars nervosa of the hypophysis and causes diabetes insipidus.

Secondly, through its connections with the rest of the brain and the spinal cord it is able to activate the sympathetic system and also, though less directly, somatic motor centers. When released from cortical control, as in Bard's preparations, or when stimulated electrically in the normal animal, the hyperactivity of the hypothalamus causes dilatation of the pupils, bristling of the hair, elevation of

the blood pressure, and on the somatic side rapid respiration, struggling, clawing and biting—in other words, the complete picture of emotional excitement. Conversely, damage to the hypothalamus produces emotional stolidity and even somnolence.

Working at least in large part through the sympathetic system, the hypothalamus serves also as a thermostat regulating body temperature.

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THE INVESTIGATION OF INTERMEDIARY METABOLISM WITH THE AID OF HEAVY HYDROGEN

Harvey Lecture, January 21, 1937

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One of the characteristics of animal life is the assimilation of food-stuffs. As the qualitative and quantitative composition of an ingested food is never the same as that of the body of the animal which consumes it, food is never deposited unchanged. Most of the split-products of the food, after their absorption, are subject to far-reaching chemical changes. Part of the compounds may be burned immediately for energy requirements but another and larger part is deposited in the organism for short or long periods. The final destruction of the carbon skeleton may occur soon, in the post-absorptive period, or much later if the compound is used as a cell constituent. In both cases, however, absorption is followed by chemical conversions.

The investigation of these processes is attended with great difficulties. The ability to interconvert metabolites is such that all constituents of the animal body, except the vitamins and a few essential dietary components, can be formed from other substances. These processes are usually very rapid and, as animals have available an abundant number of different chemical compounds, it is in many cases almost impossible to assign a definite source to a particular substance.

In the field of amino-acid metabolism Krebs, by using the method of surviving tissue slices, has recently obtained unexpected and important results. There exists, however, almost no method of carrying out studies on the interconversions of physiological substances in the living healthy and intact animal unless the end-products of such processes are disposed of in the excreta.

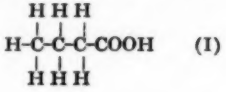
In this paper I propose to discuss experiments in which these difficulties have been circumvented by labeling the substances to be investigated by a tag which renders them recognizable in the animal body. All of the experiments which I shall discuss were carried out in collaboration with Dr. David Rittenberg.

Several attempts have been made before to use such methods for the investigation of fat transport in the animal body. One such type of experiment was to introduce bromine or other halogens into the fatty acid molecule. Thus, in working with stearic acid, animals were given a stearic acid in which one or more of the hydrogen atoms were replaced by bromine. Determination of the bromine should indicate the route taken by stearic acid in the animal. The physical and chemical properties of these halogenated fatty acids, however, are so different from those of their natural analogues that we cannot expect the cell and the organism to treat them alike. In point of fact, these artificial substances are unphysiological and are in some respects treated as foreign bodies.

In order successfully to label a compound for physiological purposes the label has to be such that its introduction does not alter the chemical and physical properties of the substance, so that the cell is unable to detect the change. The chemist, however, has to be able not only to detect the label but to analyze for it in small amounts and in high dilutions.

The only possible labels which would fulfill these requirements are the isotopes of the elements of organic substances, namely, the isotopes of carbon or hydrogen. Isotopes of the same element have identical chemical properties and even so sensitive a chemical selector as the living cell cannot distinguish between them. The only isotope which is available in amounts large enough to be used for physiological purposes is deuterium, the heavy isotope of hydrogen, discovered and isolated by Urey[1]. This heavy hydrogen has an atomic weight of two in contrast to the atomic weight, one, of normal hydrogen.

In order to label an organic substance for our purposes a part of the hydrogen of the molecule is replaced by deuterium. In the case of an acid, such as butyric acid I, this would appear to be easily accomplished. One merely has to dissolve it in heavy water. The hydrogen of the carboxyl group, which ionizes, will exchange with the deuterium of the heavy water, forming a mono-deutero-butyric acid II.



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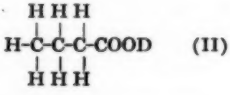

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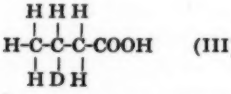

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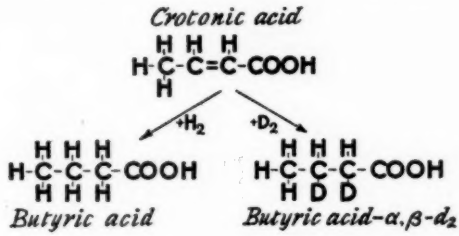
Analogous exchanges occur with the hydrogen of hydroxyl, amino, and similar groups. However, such substances in which the deuterium is exchangeable cannot be used for physiological purposes. The moment they dissolve in the water of the body fluid, which is ordinary water, they again exchange their deuterium with the normal hydrogen of the water and the deuterium is removed. It is therefore necessary to attach the deuterium directly to a carbon atom III, in the case of butyric acid to the α, β or γ carbon atom. In such a position the deuterium is stably bound and is not removed by ordinary laboratory procedures. In the course of this lecture, reference to deuterium in organic compounds always implies stable, non-exchangeable, carbon-bound deuterium.

The first question which must be considered when deuterium-containing substances are used is whether they are physiological, that is, whether the cell will treat them in the same manner as their natural analogues. There exists an indirect but definite proof that this is the case. All hydrogen obtained from any natural source, whether from

sea water, from lake water or from tap water, is a mixture of isotopes, containing ordinary hydrogen of atomic weight one with about one-fiftieth of one per cent deuterium. This composition is essentially the same in all such cases.[2,3] The same is also true of the hydrogen present in the natural organic compounds, such as sugars, fats, and amino-acids.[4,5] This means that all these natural organic compounds consist of a mixture of molecules, the majority of which contain only hydrogen of atomic weight one and a very small number of molecules which have one or more deuterium atoms. The fact that concentration or dilution of these natural deutero compounds does not take place in cells or organs is definite proof of the inability of the cell to detect them. A synthetic compound containing a higher proportion of deuterium, say one or two atoms in each molecule, cannot represent a material foreign to the living organism, as it is already accustomed to such molecules.

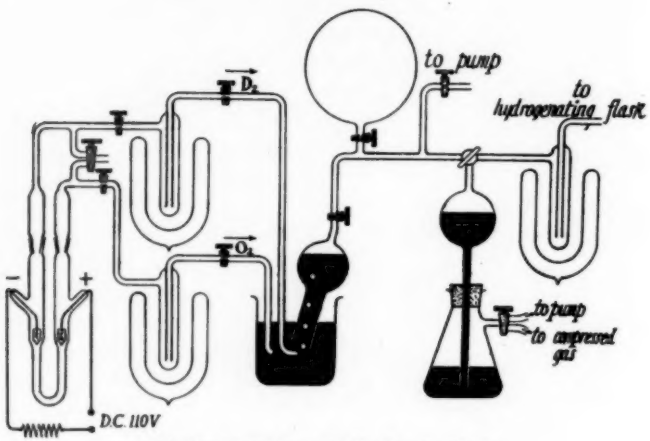
The procedure of tracing physiological compounds by the use of deuterium involves synthesis of the compounds by methods which permit the use of either pure deuterium or an isotopic mixture of abnormally high deuterium content. Numerous possibilities for such synthesis exist, the most simple and convenient of which is the catalytic hydrogenation of an unsaturated compound with deuterium gas.[6]



For instance, butyric acid may be prepared by treating the unsaturated crotonic acid with gaseous hydrogen in the presence of a catalyst like platinum, palladium or nickel. If the crotonic acid be treated with gaseous deuterium instead of hydrogen, the resulting butyric acid will contain

two atoms of deuterium, one at the α and one at the β position. As butyric acid contains eight hydrogen atoms these two deuterium atoms represent twenty-five atom per cent of the total hydrogen and on combustion the butyric acid will yield twenty-five per cent heavy water. The expression "atom per cent" will frequently occur in this paper.

Permit me briefly to describe the methods employed.[7] For the hydrogenating process the gaseous deuterium is produced by electrolytic decomposition of heavy water. This has been generously supplied by Professor Harold C. Urey, to whom Dr. Rittenberg and I are also deeply indebted for his interest and advice.



Hydrogenation with Deuterium

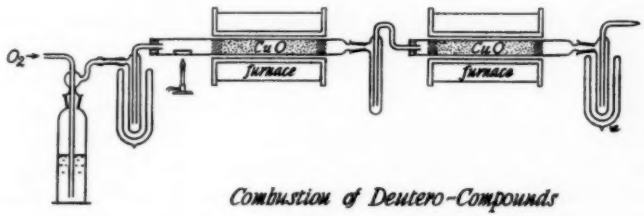
Figure 1

The heavy water is decomposed in the electrolytic cell (Fig. 1); deuterium and oxygen are passed through traps chilled to −80° in order to freeze out entrained water vapor. The oxygen bubbles through mercury into the air, while the deuterium is collected in a 5-liter flask *e*. The gas can be discharged by a Toepler pump into an evacuated hydrogenating flask, not shown in the figure, containing the

substance to be hydrogenated, together with the catalyst. The manometer indicates how much gas is present in the system at any time and how much is used up in the process.

Many pure substances, fatty acids, cholesterol derivatives, bile acids, have already been prepared by this method. As stated before, the substances are indistinguishable from their natural analogues by ordinary laboratory methods. With a few specific exceptions, which cannot here be discussed, these substances can be heated, recrystallized, or treated with acids or alkalis without any loss of deuterium.

The second method which is applied in physiological work with deuterium compounds is the analysis for deuterium in the compounds themselves or in the substances isolated from the animal after their administration. If an organic substance is burned in the laboratory the carbon forms carbon dioxide and the hydrogen forms water. If the substance contains deuterium, the deuterium will form an equivalent amount of heavy water. The deuterium analysis of organic compounds resolves itself, therefore, into the determination of heavy water in the water obtained by combustion. The combustion is carried out by a procedure similar to that used for quantitative carbon and hydrogen determinations (Fig. 2). The vapors are carried



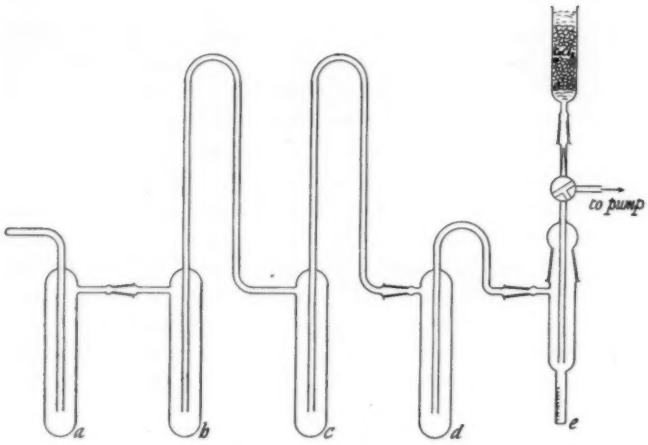
Combustion of Deutero-Compounds

Figure 2

through two tubes filled with copper oxide and heated to 750°. The water obtained is not absorbed by a hygroscopic salt but is frozen out in traps cooled to −80°. Sufficient

substance is burned to obtain 100-300 mg. of water. In the case of fats or sterols this is obtained from about the same weight of organic material.

One of the most difficult parts of the procedure is the purification of the water. That frozen out in the last trap is never pure enough for the deuterium analysis. It is necessary to distil it four times, the procedure being carried out in a closed system of a battery of five traps (Fig. 3). A minute quantity of dry chromium trioxide is



Purification of Water
Figure 3

added to the water, one arm of the trap is sealed and the other arm connected with the battery. After heating and then freezing the ice is sublimed in vacuo into the next trap containing a minute amount of dry alkaline permanganate. The water is then sublimed from one trap to another until it is finally collected in the last trap. In general, the water is now pure but to make sure, it is always necessary to repeat the whole procedure and to ascertain that the properties of the water have not changed.

The few drops of water thus obtained are used for the isotope analysis by measurement of refractive index or density according to methods which have been worked out by physical chemists and have been only slightly modified for our special purposes. All of these methods involve a comparison between the properties of the water being analyzed and those of ordinary water, which contains about one-fiftieth of one per cent deuterium. All the values given for deuterium represent, therefore, the deuterium content in excess of that of ordinary water.

The methods for heavy water determination are highly sensitive. By density measurements it is possible to determine less than 0.001 per cent heavy water. Since the physiological experiments are carried out with substances containing 1 to 10 atom per cent deuterium, which means that they form a water with 1 to 10 per cent heavy water, the substances may be diluted in the animal 1000 times or even more without our losing track of them.

On account of this high sensitivity it is possible to use the smallest laboratory mammals, namely, mice for physiological experiments with the precious substances.

Although a number of experiments on the metabolism of cholesterol[8] and bile acids[9] have already been carried out, in this paper I shall confine myself to experiments on the fate of fatty acids in the living organism. Dr. Rittenberg and I owe much to the valuable assistance of Mr. Morris Graff in the course of the physiological and chemical experiments.

The first problem undertaken was an attempt to answer the question whether fats are burned immediately after absorption, or first stored.[10] A fat prepared by partial hydrogenation of linseed oil with deuterium was administered to mice. By hydrogenating half of the double bonds so that the product contained 5.7 atom per cent deuterium, an oil was obtained the properties of which were very similar to those of olive oil. Of the many experiments which were carried out I mention only one series which may be regarded as typical. The total fat of the diet of three

mice amounted to only one per cent, consisting almost exclusively of this deutero compound. This is physiologically a very small amount. Furthermore, the total food was so restricted that the animals lost weight from undernourishment. Under these conditions it was, on the basis of our former ideas, to be expected that the animals would burn all the fat immediately after consumption. But this was not the case. At the end of a four-day period the animals were killed, the fat of the fat tissues was isolated and the deuterium content of the fatty acids determined (Table I).

FEEDING THREE MICE A DIET CONTAINING
1% DEUTERO-FAT (5.74 ATOM % D)
(Duration of experiment four days)

Deutero-fat consumed	Deutero-fat recovered in fat tissue	Per cent of diet fat stored in fat tissue	Burned diet fat recovered as heavy water
251 mg.	119 mg.	47%	20%

Table I

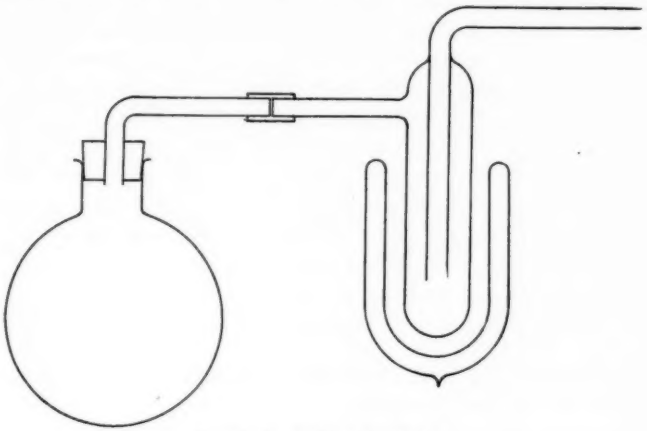
The animals had consumed in the experimental period 251 mg. of diet fat. Of this fat there was recovered from the fat depots an amount of deuterium corresponding to 119 mg. or forty-seven per cent of the diet fat, an unexpectedly high percentage.

From these and many analogous experiments the conclusion was inescapable that the larger part of the dietary fat, even when given in small amounts together with other foodstuffs, is first deposited in the fat tissues and is not oxidized directly. I shall discuss later the physiological implications of this finding.

Of the fat given to the animals about half, namely forty-seven per cent, was recovered. The other part had obviously been burned in the animal. The use of deuterium as a label also furnishes a means for determining the rate and the amount of degeneration in the organism.

As I have stated, deuterium-containing substances when burned in the laboratory form an equivalent amount of heavy water. Heavy water is also formed when the combustion takes place in the animal. It will mix with the

body fluids and, as no organ can concentrate or dilute it, the water of all body fluids will have the same composition. In order to measure the deuterium in the fluids any water from the animal may be used. In work with mice the total carcass before chemical treatment is put into a flask connected with a trap cooled to −80° (Fig. 4). The system is



Distillation of Body Fluids

Figure 4

evacuated, whereby the animal freezes and the water sublimes into the trap. This water after purification is subjected to deuterium analysis. This procedure is carried out in almost all experiments in order to determine the extent of degradation of the deutero substances fed.

In the series which I have just mentioned the water of the body fluids contained an amount of deuterium equivalent to twenty per cent of the ingested fat. About fifty per cent of the deuterium consumed with the fatty acids was recovered in the fat tissues and twenty per cent in the water. The remaining thirty per cent of the deuterium was probably excreted as water in the urine, feces and breath. We have not yet attempted to run a total water balance which

would be necessary to follow quantitatively the combustion of deuterium-containing substances.

The experiments leave unanswered the question whether the fatty acids in the fat tissues, which are derived from the diet, are still the same unaltered chemical individuals administered with the food. Various foods may change the properties of the depot fat somewhat but only to a limited extent. Animals have a tendency to form, independent of the quality of the food, a depot fat the properties of which are characteristic for the animal species and depend upon the quantitative distribution of the component fatty acids. An animal given fat in its food may have two theoretically possible mechanisms at its disposal for producing from the dietary fat its own characteristic depot fat. It may either transform the ingested fatty acids or it may synthesize from other compounds just those fatty acids needed to confer upon the depot fat its characteristic properties. Both hypothetical mechanisms, namely, the interconversion of fatty acids and their new formation from other sources, must be investigated to obtain an insight into the fate of fats after their absorption.

The natural fatty acids are usually classified into saturated and unsaturated acids, dependent upon the occurrence of double bonds. This classification is interesting from the standpoint of both chemistry and physiology. The saturated acids, the most important of which are stearic and palmitic acids, are high-melting substances and their presence in combination with glycerol gives the fats a solid consistency. The unsaturated acids, for example oleic acid, are fluids at room and body temperatures and render the fats oily. All natural fats contain varying amounts of both classes of fatty acids.

A mechanism whereby the degree of saturation could be varied would enable the animal to give the tissue fat any necessary consistency. For about seventy years physiological literature has contained discussions of the possibility of the biological desaturation of fatty acids, an example of which would be the biological formation of oleic

acid from stearic acid. Although no definite proof for this biological conversion has yet been given, the majority of investigators believe in its occurrence and a number of them postulate it to be the first step in biological fatty acid degradation. Acceptance of this view, however, is far from general; for instance, Drummond,[11] in his Harvey lecture of 1933, after critically surveying the known material, definitely questioned the occurrence of such a process in the animal.

The investigation of conversions of organic compounds in the animal organism can conveniently be carried out with the aid of deuterium. If a deutero substance, A, is given to the animal and another substance, B, also containing deuterium is isolated from the animal body, B must have been derived from A. For such investigations it is necessary to give the animal a pure chemical compound rather than an undefined fat mixture, such as the oil which was used in the first experiments on fat transport.

To investigate the desaturation of fatty acids,[12] several series of mice were fed the saturated fatty acid, stearic acid, which was obtained by hydrogenation of linoleic acid with deuterium. This stearic acid contained about eight atom per cent deuterium. In the one series which I shall here discuss three animals were fed for twelve days with a diet containing ten per cent of this deutero-stearic acid. At the end of the procedure the animals were killed and the total fatty acids of the carcass were isolated (Table II).

ISOLATION OF UNSATURATED FATTY ACIDS FROM MICE FED SATURATED ACIDS (8.66 ATOM % D)

	Deuterium content
Total fatty acids	1.70 atom % D
Saturated acids	2.58 " " "
Unsaturated acids (oleic acid)	1.16 " " "

Table II

The total acids, which contained 1.7 atom per cent deuterium, were fractionated by a procedure especially developed for this problem. The saturated fatty acids contained 2.58 atom per cent deuterium; the high deuterium content of this fraction is obviously due to storage of the saturated fatty acids ingested. The unsaturated fatty acids which, according to the iodine number, consisted mainly of oleic acid, had 1.16 atom per cent deuterium, conclusive evidence of their origin from the administered deutero-stearic acid. This experiment clearly proves the ability of mammals to desaturate fatty acids.

From these findings the question arose as to whether the mice were also able to perform the reverse chemical reaction, namely, the saturation of unsaturated acids. For such experiments mice had to be fed a deuterium-containing analogue of oleic acid or other natural unsaturated acid. While it was easy to prepare deutero-stearic acid in the laboratory, we were unsuccessful in synthesizing deutero-oleic acid. All attempts yielded mixtures which contained several isomers of oleic acid and we did not wish to feed these since they are not physiological substances.

If synthesis of a deutero compound does not succeed in the laboratory it is in many cases possible to obtain it by biological preparation. I have just reported the isolation of a deuterium-containing oleic acid formed by mice from deutero-stearic acid. This oleic acid contained over one atom per cent deuterium, a concentration large enough for feeding experiments. The material was fed to other mice, from which in turn the total fatty acids were isolated and fractionated (Table III). The saturated fatty acids con-

SATURATION OF FATTY ACIDS

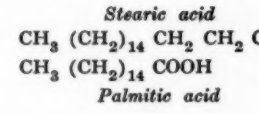
Experiment number	Atom % D in unsaturated acids	Atom % D in saturated acids
1	0.25	0.047
2	0.10	0.025

Table III

tained an amount of deuterium clearly indicative of their origin from the unsaturated acids consumed, in spite of the fact that the deuterium present in the original stearic acid was highly diluted by the two animal passages. These saturated, deuterium-containing fatty acids had an interesting history. They were first prepared in the laboratory in the form of stearic acid, desaturated by one group of mice to oleic acid and in turn saturated by another group of mice.

These experiments show that saturation and desaturation is a biologically reversible process; the animal is able to convert oily fatty acids into high-melting ones and vice versa, and, by the same token, to convert food fats into body fats of any consistency.

The fatty acids may undergo other conversion processes besides saturation and desaturation. The saturated high-melting fatty acids of the mammalian fats are mainly mixtures of two acids of very similar properties, namely, stearic and palmitic acids, containing eighteen and sixteen



carbon atoms respectively. The question arises whether the organism is able to convert stearic into palmitic acid, a reaction which involves shortening of the chain by two carbon atoms. The pioneer work on β-oxidation by Knoop and by Dakin suggests that such a reaction may take place. However, no methods have been available for investigating this particular process and, to the best of our knowledge, no such study has ever been attempted.

The procedure here followed was in principle the same as that of the experiments just described. Mice were fed pure deutero-stearic acid and from their carcasses the mixtures of saturated acids were isolated. The acids were converted into the methyl esters and the palmitic and stearic acid esters were separated by repeated fractional

distillation (Table IV). The deuterium content of the isolated palmitic acid proved definitely its origin from the stearic acid administered.

DEUTERIUM CONTENT OF FATTY ACIDS OF MICE AFTER FEEDING DEUTERO-STEARIC ACID (7.13 ATOM % D)

Stearic acid	Palmitic acid
2.6 atom % D	0.33 atom % D

Table IV

All these experiments on conversion of fatty acids substantiate the aforementioned hypothesis that the dietary fatty acids may be converted into other acids necessary to give the depot fats such properties as are characteristic of the species. These interconversions, however, represent only one chapter in the formation of depot fat. Another even more complex one is the synthesis of fatty acids from food materials other than fats. The occurrence of such animal synthesis from sugars has long been established in the case of overfeeding and plays a rôle in the fattening of animals with carbohydrates.

Synthesis of fats has previously been measured only by indirect methods, such as balance experiments, and was recognized only when the animals put on more fat than was administered with the diet.

Deuterium represents a tool that can also be employed generally for the study of synthetic processes in the animal body. If an organic substance is synthesized in the laboratory in a medium of heavy water instead of ordinary water, the deuterium of the heavy water may enter the reaction and be found in the product synthesized. This is a principle which is frequently used for the preparation of deutero substances in the laboratory.

If the body fluids of an animal contain heavy water, synthetic processes in the animal will, just as in the laboratory, lead to products containing deuterium. Heavy water may thus be used as a general indicator for synthetic processes in animals.

For experiments of this kind[13] mice were first injected with an amount of concentrated heavy water just sufficient to raise the heavy water content of the body fluids to a concentration of 1.5 per cent. In order to maintain the body fluids of the mice at this heavy water concentration, the mice were given 2.4 per cent heavy water to drink instead of ordinary water. This was found in preliminary experiments to be the proper concentration for keeping the body fluids at 1.5 per cent. The drinking water has of course to have a higher concentration as it will be diluted in the animal by the ordinary water formed by the combustion of food material. So from the moment of heavy water injection all synthetic processes in the mice took place in a medium of about 1.5 per cent heavy water. In the experiments now to be reported the mice received a basic diet of bread, which was practically devoid of fat (Table V).

DEUTERIUM CONTENT IN BODY FLUIDS AND FATTY ACIDS OF MICE GIVEN HEAVY WATER

Experiment number	Duration of experiment	Deuterium in body fluids	Deuterium in fatty acids
	days	atom per cent	atom per cent
1	3	1.21	0.11
2	4	1.09	0.08
3	6	1.43	0.21
4	9	1.50	0.20
5	19	1.51	0.22

Table V

Five series of three mice were killed at different intervals and water and fats were isolated from the carcasses and analyzed for deuterium. While in the first days of the experiments the heavy water concentration in the body fluids varied somewhat, it was constant after six days. The deuterium content of the fatty acids rose rapidly and attained a maximum after about six days and continuation of the experiments up to even nineteen days brought about no increase over the concentration at six days.

If the uptake of deuterium into the fatty acids indicates a new synthesis of fatty acids, the experiment means that

the fatty acids of mice on a carbohydrate diet are replaced after six days by new fatty acids which are now characterized by a content of 0.21 atom per cent deuterium. As the animals did not gain or lose weight and therefore must have kept their total amount of fat constant, there must have occurred with the synthesis a simultaneous breakdown of an equivalent amount of fatty acids.

In order to demonstrate this breakdown the reverse experiment was carried out: instead of giving mice heavy water to drink, eight groups of three mice each received deuterium-containing fatty acids and bread, together with ordinary water. The deutero-fatty acids were partly stored in the fat depots as was pointed out in all the former experiments. Thus, the fat depots were labelled by deuterium. After five days of this diet the five control groups had an average deuterium content of 0.93 atom per cent deuterium in their depot fats (Table VI). The remaining

DEUTERIUM CONTENT OF FATTY ACIDS OF MICE AFTER DISCONTINUATION OF FAT FEEDING

Expt. no.	Days on fat free diet	Combined wt. of animals gm.	D_2 in fatty acids Atom %	
1		57	0.97	Controls
2		59	0.90	
3		59	0.72	
4		57	1.05	
5		65	1.02	
		Average	0.93	
6	2	56	0.66	
7	4	57	0.35	
8	6	65	0.13	

Table VI

three groups of mice were now continued on the same diet without the fat, that is, on bread and ordinary water. The deuterium content of the depot fat of these animals now decreased rapidly and after six days on the bread diet only about 15 per cent of the original deuterium remained. A rapid destruction of the fatty acids had thus occurred.

If the results of the last two experiments are plotted together, the first experiment in terms of fatty acid synthesis and the second in terms of fatty acid destruction, both curves run almost parallel (Fig. 5), indicating that in

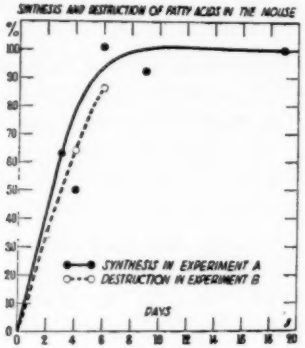


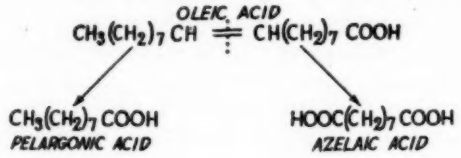
Figure 5

both experiments we had measured the same process, namely, the turnover of fatty acids in mice on a carbohydrate diet. According to the findings, mice on a bread diet continuously form and destroy fatty acids, and after about six days new fatty acids have replaced the old ones. The average half lifetime, under the above conditions, of the fatty acids in the mouse is less than three days.

The methods were so new and the results so unexpected that a number of other experiments had to be performed to make sure that what had been measured was actually a turnover of fatty acids and not some other process which might have brought about the same results. One such possibility was the following: saturation and desaturation of fatty acids is, as above stated, a biologically reversible process. This process may go on in the organism continuously. If the double bonds of unsaturated acids are saturated in a medium containing heavy water, deuterium must enter into the molecule. If this process takes place in an animal the body fluids of which contain heavy water, as in the

first experiment, the saturated acid may also acquire deuterium. Conversely, a deuterium-containing fatty acid when desaturated may lose deuterium, as in the second experiment. The question arose whether the findings might not just as well have been the result of repeated saturation and desaturation rather than of a turnover of the fatty acids.

That saturation and desaturation were not responsible for our results could be proved by investigating the chemistry of the newly formed fatty acids. All the unsaturated fatty acids of the mammalian organism which contain sixteen and eighteen carbon atoms have one double bond between C_9 and C_{10}. In the acids with more double bonds, such as linoleic and linolenic acids, the other double bonds are situated in the part of the chain remote from the carboxyl group. The part of the molecule between the carboxyl group and C_9 is always saturated and never contains double bonds. Therefore, all the unsaturated acids, like oleic acid, form azelaic acid on oxidation. If the part of the fatty acid



molecule represented by the azelaic acid contains deuterium, the latter could not have entered the molecule by a process of hydrogenation but must have entered by another mechanism. From the deuterium-containing fatty acids which were formed by the mice which drank heavy water, the unsaturated fatty acids were isolated, ozonized, and subsequently oxidized. The azelaic acid obtained in pure form contained the same percentage of deuterium as the total fatty acid from which it was split off. This deuterium could not have entered by saturation of double bonds since this part of the molecule, as already stated, never contains a double bond. Hydrogenation and dehydrogenation could,

therefore, not have been responsible for the results of these two experiments.

There still existed one other possibility that may have been responsible for the findings. The deuterium-containing substances which were fed to the animals and those which were isolated from the bodies, all had their deuterium in stable linkage. Such substances can be heated to high temperatures, treated with strong acids or alkalis, etc., without any loss of their deuterium, and their stability in the organism was to be expected. But if there existed in the body an enzyme which labilizes carbon-bound hydrogen so that the deuterium may exchange with the hydrogen of the solvent, in our case the body fluids, such an enzymatic exchange might have led to similar results. As nothing was yet known about such enzymes, experiments had to be carried out to exclude their occurrence.

The most convenient procedure for such investigation is to keep living organs in contact with heavy water and to determine whether deuterium enters organic molecules in stable positions. Mammals are not suitable for such studies. They have to be fed, and if their body fluids contain heavy water the conversion of food into other constituents will in itself lead to the uptake of deuterium. A suitable organism must not ingest food but must have an active metabolism and live for a considerable time. The developing hen's egg was used for this purpose.

Fertilized eggs were injected at the first day of development with an amount of heavy water sufficient to bring the concentration of heavy water up to one per cent, a level which persisted to the end of the experiment. The eggs were then incubated; after twenty days, immediately before hatching, the chicks were removed and the fatty acids isolated. If a labilizing enzyme were present in the eggs, the fatty acids should contain deuterium, introduced by exchange with the deuterium of the cell water. But the fatty acids of the chicks contained not a trace of deuterium above the normal level.

These facts exclude with certainty the presence in eggs of an enzyme which labilizes carbon-bound hydrogen in fatty acids. And as in general the enzymes of chicks are the same as in mammals, we feel justified in excluding its presence also in mice. The finding furthermore establishes the interesting fact that no turnover of fatty acids takes place in developing eggs. The egg utilizes the fatty acids already present but no new fatty acids are formed. It was later found that the same is true of the cholesterol, which is not only not synthesized but also not destroyed by the developing egg.

The chicks which developed in dilute heavy water were indistinguishable from the normal control animals. This finding is of interest in connection with the theory postulated by several investigators that even small concentrations of heavy water have a marked influence on the total metabolism of the cell. If this were the case a difference should have been noticeable. In general, while it seems certain that high concentrations, namely, over thirty per cent, influence the rate of physiological reactions, none of our numerous experiments with heavy water in low concentrations gave the slightest indication of any effect.

All five experiments together show that in mice on a carbohydrate diet the fatty acids have a surprisingly rapid turnover. They are continuously decomposed and resynthesized, and under our conditions this process was completed within about six days.

The question arises as to the source of the newly formed fatty acids. Our animals received mainly carbohydrates and only a minimum of protein. The large amounts of fatty acids which were synthesized must have been derived from the carbohydrates of the food.

As already mentioned, it has been known for a long time that carbohydrates may be converted into fats by higher animals under the condition of overfeeding or fattening. The new experiments show that this conversion occurs not only under these extreme conditions but also on a normal diet.

We are certain that this process takes place not only in mice but occurs in all animals. However, we do not wish to suggest that the turnover always occurs within six days. It must depend upon the species of animal and the conditions under which the animals are kept. It is probably faster in small animals, which have a more rapid metabolism than larger ones.

The only explanation which we can offer for this turnover is the following: Animals do not eat continuously but at intervals. At each meal the animal has to consume an excess of food for utilization during the post-absorptive period. Part of the excess carbohydrates and amino-acids is deposited in the organs in the form of glycogen; but the capacity for glycogen deposition, especially in small animals, is strictly limited. The larger part of the excess carbohydrate is immediately converted into fats and stored in the fat tissues. During the post-absorptive period, after the glycogen has been consumed, energy is supplied by the oxidation of fatty acids liberated from the depots.

The fat tissues are generally regarded as a storage for time of need and have frequently been compared with a dead storage or food cellar for emergencies. On the basis of the new findings the fat tissues might better be compared with the refrigerator in which excess food is stored for the short periods between meals. If a less homely comparison be desired, the fat depots may be regarded as a biological energy buffer. During absorption they take up in the form of fats excess food material not immediately used for energy requirements. Conversely, during the post-absorptive period they supply fats to make up the energy deficit.

Contrary to the general idea of the slow metabolism of fat tissues, all the experiments above outlined point to the fact that the fat stores are very actively involved in the conversion processes characteristic of life. It would be highly interesting to know whether there exist any diseases in which one or the other of the reactions mentioned is disturbed. Investigations along such lines may throw light on some diseases of fat metabolism.

Deuterium has given us an insight into the far-reaching changes undergone by fatty acids in animals under normal dietary conditions. The various acids are continually interconverted into one another, are degraded and replaced by new acids, without necessarily any change in the total fat content of the animal. Analogous measurements on cholesterol in mice have shown that this complex organic molecule is subject to almost the same process as the fatty acids, that is, to a continuous degradation and synthesis. It can already be predicted with a high degree of probability that the same will be found true of many if not all of the other organic constituents of the animal body.

It has long been recognized that the morphological units of the living tissue, namely, the cells, have also a brief lifetime. They are continuously being replaced by new and identical cells, while the tissue as a whole maintains, with limited variations, its characteristic structure. In analogy to this, there is a similar continuous destruction and replacement of the various organic chemical molecules in the living animal. What is especially striking is that this occurs even with those substances which had previously been assumed to serve only as reserve material and not to be actively involved in the general metabolism.

To preserve the structure of a tissue at a given moment it is necessary to interrupt the cellular replacement process by removing the tissue and to fix it by the usual histological technique. Attempts to preserve the chemical constituents at a given instant must follow analogous lines. The chemical substances when isolated from an organism may be kept unchanged indefinitely. However, as long as they remain actual constituents of the living body, they represent links in a chain of continuous reactions in which apparently all organic substances, even those of the storage material, are involved. It is with this aspect of the organic molecule as an active component of the dynamic processes of life that the biochemist is especially concerned. The isotopes of those elements which are present in natural organic compounds, presented to the biologist

by the physical chemist, will certainly furnish a better insight into the details of this intricate mechanism.

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THE ACADEMY SCHOLARSHIPS

Mrs. Elizabeth Cochran Bowen has again provided the Academy of Medicine with funds for maintaining two Scholarships, each for one year's study in European clinics. These Scholarships are open to recent graduate internes of municipal or voluntary hospitals of New York City who wish to prepare themselves for the practice of clinical medicine or surgery in any of their branches.

In former years Mrs. Bowen desired that the two Scholarships be designated the Alexander Cochran Bowen Scholarships. This year, however, she has indicated her wish that one be called the Alexander Cochran Bowen, and the other, the Harlow Brooks, in memory of that great and well-beloved Fellow of this Academy.

1. FURTHER STUDIES ON THE INTRAPERITONEAL USE OF BOVINE AMNIOTIC FLUID IN ABDOMINAL SURGERY

J. Randolph Geppert
Melvin L. Stone

The authors report the results of the use of Amfetin administered intraperitoneally at the time of operation in a series of one hundred and two gynecological celiotomies. One hundred twenty-five patients having similar operations, but not having Amfetin administered were used as controls. The study was chiefly one of post-operative reaction in treated and untreated patients. The conclusions reached were that the intraperitoneal administration of Amfetin showed no appreciable effect on blood pressure, pulse, temperature or wound infection, but that normal intestinal motility and normal contraction of the bladder seems to return sooner in the treated patients. It is felt that the use of Amfetin at the time of operation holds definite promise of affording the patient some degree of relief from nausea, vomiting, gas pains and distention. The question of prevention of adhesions was not considered in this study.

2. A HISTOLOGIC DIAGNOSIS OF PREGNANCY

Bertram G. Smith, Ph.D.
Endre K. Brunner

The vaginal epithelium may be subdivided into 3 distinct layers—the squamous faintly stained superficial—the squamous darkly stained middle or cornified—and the thick basal layer which corresponds with the stratum germinativum of the skin.

The basal layer is the seat of characteristic changes during pregnancy. The distal portion of the basal zone which is normally made up of lightly stained polyhedral cells will become thicker, and the cells more numerous. The individual cells are larger and the amount of vacuolation roughly twice as great as in the non-pregnant woman.

These changes are present in all age groups and as early as when the patient is within one week overdue.

The material was obtained by biopsies taken without anesthesia, the size not exceeding 3 mm. Serial sections were made and stained with haematoxylen and eosin. The study was based on 155 biopsies from 79 cases of pregnancy or suspected pregnancy. In 21% of cases the vaginal epithelium was the seat of chronic inflammation which prevented us from making any other histologic diagnosis. Some of those were later proven non-pregnant.

Because of its rapidity, this method might be successfully employed as an additional aid in the diagnosis of extrauterine pregnancy.

3. RESULTS OF THERAPY IN THE LUETIC ANTEPARTUM CLINIC AT BELLEVUE HOSPITAL

MORTIMER D. SPEISER

Efficient treatment can best be given in a "Prenatal Syphilis Clinic" properly equipped and staffed. A scheme of treatment is outlined depending upon the stage of the syphilitic infection and the length of gestation. Antepartum treatment not only reduces the incidence of premature deliveries but also the incidence of breech presentations. Postpartum morbidity is exceedingly high in patients with genital lesions who have received no treatment. Treatment in a similar group of patients reduces this incidence. Maceration and early deaths of offspring were fifteen times more frequent in patients who received no treatment as compared with those who received treatment both before and during pregnancy. Syphilitic live children occurred twelve times more often in the untreated group compared with the well treated group. It is never too late in pregnancy to bring about some good by the use of antisyphilitic therapy. Arsenicals given the pregnant woman are attended with an increased risk of reactions. Gastro-intestinal reactions, pruritus and icterus lead the list in frequency. While mild reactions are of almost equal prevalence in white and colored patients, severe reactions are encountered with greater frequency in the former group.

A SELECTION OF RECENT ACCESSIONS

"Possession does not imply approval"

MARCH

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Randall, L. The famous cases of Sir Bernard Spilsbury.
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Walters, R. C. S. The nation's water supply.
London, Nicholson, 1936, 244 p.

MEMBERS ELECTED MARCH 3, 1937

Lester Blum ..... 500 West End Avenue

William Leifer ..... 286 West 86 Street

Olga R. Povitzky ..... 72½ Irving Place

Jose A. Presno y Bastiony ..... 19 esq. a Paseo, Vedado, Habana, Cuba

Louis Schwartz ..... 390 Riverside Drive

William Snow ..... 25-10 Butler Street, East Elmhurst, L. I.

Solomon Weintraub ..... 240 East 79 Street

APRIL 1, 1937

Charles Haines.....421 Hugenot St., New Rochelle
Alexander Altschul.....350 Central Park West
John G. McGrath.....501 Madison Avenue
John Warren Rogers.....201 East 40 Street
Arthur A. Rosenthal.....322 Central Park West
William Thalhimer.....30 Beekman Place
James R. Beard, Jr.....8 West 16 Street
Phineas Bernstein.....2 East 85 Street
Linn John Boyd.....58 Burkewood Rd., Mt. Vernon

PROCEEDINGS OF ACADEMY MEETINGS

MARCH

STATED MEETING

THE NEW YORK ACADEMY OF MEDICINE—March 3

I. EXECUTIVE SESSION—a. Reading of the Minutes.

II. PAPER OF THE AFTERNOON—Significance of Serologic Tests in Syphilis, A. Benson Cannon, Associate Professor of Dermatology, College of Physicians and Surgeons.

III. REPORT ON ELECTION OF MEMBERS.

March 18

THE HARVEY SOCIETY (IN AFFILIATION WITH THE NEW YORK ACADEMY OF MEDICINE)

THE SIXTH HARVEY LECTURE, "The Control of Excitation in the Nervous System," Herbert S. Gasser, Director, Rockefeller Institute for Medical Research.

SECTION MEETINGS

SECTION OF DERMATOLOGY AND SYPHILOLOGY—March 2

I. READING OF THE MINUTES.

II. PRESENTATION OF CASES—a. New York Polyclinic Hospital; b. City Hospital; c. Miscellaneous cases.

III. DISCUSSION OF SELECTED CASES.

IV. EXECUTIVE SESSION—Appointment of Nominating Committee.

COMBINED MEETING OF THE NEW YORK NEUROLOGICAL SOCIETY AND SECTION OF NEUROLOGY AND PSYCHIATRY—March 2

I. PAPERS OF THE EVENING—a. The organic syndrome in the psychoses, Samuel W. Hamilton (by invitation); b. Constitutional factors in the paranoid psychoses, Nolan D. C. Lewis (by invitation); c. An evaluation of the biochemical approach to the psychoses, William H. Dunn (by invitation); Discussion: Karl M. Bowman (by invitation); Wendell Muncie, Baltimore (by invitation).

SECTION OF SURGERY—March 5

I. READING OF THE MINUTES.

II. PRESENTATION OF CASES—a. Cases of giant cell tumor of the long bones, Norman L. Higinbotham; b. 1. Suppurative arthritis of knee joint with osteomyelitis. Resection of joint and fusion; 2. Popliteal bursitis connecting knee joint. Two cases, Condict W. Cutler, Jr.; c. Spontaneous healing of gangrene of lower extremity, Saul S. Samuels.

III. PAPERS OF THE EVENING—a. The causal relationship of thromboangiitis obliterans and typhus fever, Charles Goodman; b. Human bite infections of the hand, Roland L. Maier (by invitation).

IV. General Discussion.

V. Executive Session—Appointment of Nominating Committee.

SECTION OF HISTORICAL AND CULTURAL MEDICINE—March 10

I. Executive Session—a. Reading of the Minutes; b. Nomination of Section Officers and one Member of Advisory Committee.

II. Papers of the Evening—a. Jonathan Hutchinson: The last of the multispecialists, Gordon M. Bruce; Discussion: Beeckman J. Delatour; b. William Henry Perkin; with exhibit of books, Herman Goodman; Discussion: Victor Robinson (by invitation).

SECTION OF PEDIATRICS—March 11

I. Papers of the Evening—Program from the Department of Pediatrics, Yale University: a. An immunological comparison of six strains of the virus of poliomyelitis, J. D. Trask (by invitation), J. R. Paul (by invitation); Discussion: Thomas M. Rivers, S. D. Kramer (by invitation); b. 1. Factors controlling the distribution of body water, Daniel C. Darrow (by invitation), Herman Yannet (by invitation); 2. Changes in distribution of body water in artificial fever, Herman Yannet (by invitation), Daniel C. Darrow (by invitation); Discussion: Samuel Z. Levine, A. A. Weech (by invitation).

II. Executive Session—Appointment of Nominating Committee.

SECTION OF OPHTHALMOLOGY—March 15

Program arranged by the Institute of Ophthalmology, Presbyterian Hospital

Instructional Hour, 7:00 to 8:00 p. m.—Contact glasses, Gordon M. Bruce.

Demonstrations, 7:30 to 8:30 p. m.—a. Photography, Laurance Redway (by invitation); b. Fundus pictures, Gustav Bethke (by invitation); c. Instrument for detached retina operations, Kern Larkin (by invitation); d. Anatomical variations in the optic canal, Raymond Pfeiffer.

REGULAR PROGRAM

I. Executive Session—a. Reading of the Minutes; b. Appointment of Nominating Committee.

II. Presentation of Cases—a. Surgery of the cornea, Ramon Castroviejo; b. Essential atrophy of the iris, Hugh S. McKeown; c. Treatment of tobacco alcohol amblyopia, Frank D. Carroll (by invitation).

III. Papers of the Evening—a. Studies on chronic catarrhal conjunctivitis. Preliminary report, Philips Thygeson (by invitation); b. Orbital cysts without epithelial lining, John M. Wheeler.

COMBINED MEETING OF THE NEW YORK HEART ASSOCIATION AND THE SECTION OF MEDICINE—March 16

I. Executive Session—Section of Medicine—a. Reading of the Minutes; b. Appointment of Nominating Committee.

II. Papers of the Evening—a. Cardiac dyspnea, Tinsley Harrison, Nashville, Tennessee (by invitation); Discussion: Harold J. Stewart, Dickinson W. Richards, Jr. (by invitation); b. Cardiac diseases—nosology and the public health, Alfred E. Cohn; Discussion: John Wyckoff.

III. General Discussion.

SECTION OF GENITO-URINARY SURGERY—March 17

I. Executive Session—a. Reading of the Minutes; b. Appointment of Nominating Committee.

II. Case Reports—a. "The vena cava—bifurcated by the ureter." Autopsy specimen, Fedor L. Senger; b. "A consideration of ureteral anomalies with special reference to partial duplication with one branch ending blindly: A report of two cases with renal obstruction cured by surgical resection," Augustus Harris.

III. Papers of the Evening—a. Conservative management of damaged renal tissue, Jefferson C. Pennington and Earl C. Lowry, Nashville, Tennessee (by invitation); b. Diabetes in surgical urology, John Duff, Frederick W. Williams; Discussion opened by: Edwin T. Hauser; Discussion: Joseph Hyams, Robert Gutierrez, J. Sturdivant Read.

IV. General Discussion.

SECTION OF OTOLARYNGOLOGY—March 17

Held at the College of Physicians in Philadelphia

The Section was the guest of the Section of Otolaryngology of the College of Physicians.

I. Executive Session—a. Reading of the Minutes; b. Appointment of Nominating Committee.

II. Papers of the Evening—a. Acute leukemic labyrinthine disease, Horace J. Williams; b. Significance of experimental otology, Walter Hughson (by invitation); c. Bronchoscopy in the management of postoperative pulmonary complications, Gabriel Tucker; Discussion opened by: Page Northington, Edmund Prince Fowler, Charles J. Imperatori, Marvin Jones, John D. Kernan, John M. Loré.

SECTION OF ORTHOPEDIC SURGERY—March 19

I. Executive Session—a. Reading of the minutes; b. Appointment of Nominating Committee.

II. Paper of the Evening—A new approach to the problem of low back pain, Horace C. Pitkin, San Francisco (by invitation); Discussion: Loring T. Swaim, Boston (by invitation); Walker E. Swift, Lewis Clark Wagner.

III. General Discussion—Leo Mayer, Mather Cleveland.

SECTION OF OBSTETRICS AND GYNECOLOGY—March 23

Program presented by the Obstetrical and Gynecological Service, of Bellevue Hospital

I. Case Presentation—a. A case of adenomyosis in a primipara resulting in spontaneous rupture of the uterus at the onset of labor, Melvin L. Stone (by invitation).

II. Papers of the Evening—a. Further studies on the intraperitoneal use of bovine amniotic fluid in abdominal surgery, J. Randolph Gepfert (by invitation), Melvin L. Stone (by invitation); Discussion: R. Sterling Mueller (by invitation), John Jacob Westermann, Jr.; William Seaman Bainbridge; b. A histologic diagnosis of pregnancy, Endre K. Brunner (by invitation); Discussion: Bertram G. Smith, Ph.D.; Samuel H. Geist; c. Results of therapy in the luetic antepartum clinic at Bellevue Hospital, Mortimer D. Speiser; Discussion, Alfred C. Beck, Thurman Boyd Givan (by invitation), Walter Clarke (by invitation).

III. Executive Session—Appointment of nominating committee.

AFFILIATED SOCIETIES

NEW YORK ROENTGEN SOCIETY *in affiliation with* THE NEW YORK ACADEMY OF MEDICINE—March 15

I. 8:00-8:15 Presentation of Interesting Cases.

II. Papers of the Evening—a. Pathogenesis of tuberculosis, Harry Wessler (by invitation); Discussion opened by: J. Burns Amberson, Jr. (by invitation), Paul Klemperer (by invitation), Ross Golden; b. The oblique projection of the thorax; an anatomic and roentgenologic study, Carleton B. Peirce (by invitation); Discussion opened by: Dickinson W. Richards, Jr. (by invitation), Richmond L. Moore (by invitation); Bruce W. Stocking (by invitation), George J. Plehn.

III. Executive Session.

NEW YORK MEETING OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE—March 17

I. The production of specific enzymes by micro-organism, Rene Dubos, Rockefeller Institute.

II. The relation of calcium to protein in hyperproteinemia, A. B. Gutman and E. B. Gutman, College of Physicians and Surgeons.

III. Distribution in body fluids of ingested potassium chloride and ammonium chloride and their mode of excretion, Jacques Bourdillon, Rockefeller Institute.

IV. Certain factors involved in the correlation between age and organ response to hormonal stimulation, Earl T. Engle, College of Physicians and Surgeons.

NEW YORK PATHOLOGICAL SOCIETY *in affiliation with* THE NEW YORK ACADEMY OF MEDICINE—March 25

NOTICE—As the annual meeting of the American Association of Pathologists and Bacteriologists was held in Chicago on the date of the regular meeting of the New York Pathological Society, no meeting of the Pathological Society was held in March.

DEATHS OF FELLOWS

GOLDENBERG, HERMANN, M.D., 128 East 72 Street, New York City; graduated in medicine from the Royal Bavarian University of Munich in 1886; elected a Fellow of the Academy April 2, 1891; died April 1, 1937.

Dr. Goldenberg held a certificate from the American Board of Dermatology and was consulting dermatologist to the Mount Sinai and Bronx Hospitals. He was a Fellow of the American Medical Association and a member of the County and State Medical Societies.

JARECKY, HERMAN, A.B., M.D., 120 West 86 Street, New York City; received the degree of Bachelor of Arts from the College of the City of New York in 1883, and graduated in medicine from the College of Physicians and Surgeons in 1886; elected a Fellow of the Academy June 7, 1900; died March 14, 1937.

Dr. Jarecky had been consulting otolaryngologist to the Sydenham Hospital. He was a member of the American Academy of Ophthalmology and Otolaryngology, the Alumni Association of City Hospital, the American Medical Association and the County and State Medical Societies. He was the author of various papers on diseases, operations and treatment of eye, ear, nose and throat.

SPIES, EDWIN ALBERT, M.D., 24 East 36 Street, New York City; graduated in medicine from Fordham University School of Medicine in 1910; elected a Fellow of the Academy November 2, 1922: died March 21, 1937.

Dr, Spies, at the time of his death, was adjunct professor of orthopedic surgery at the New York Polyclinic Medical School and Hospital; orthopedic surgeon to the Morrisania and Misericordia Hospitals and consulting orthopedic surgeon to St. Francis' Hospital, Poughkeepsie, He held a certificate from the American Board of Orthopedic Surgery.

Dr. Spies was a Fellow of the American College of Surgeons, the American Medical Association and a member of the State and County Medical Societies.

THE GRADUATE FORTNIGHT

The subject of the Tenth Annual Graduate Fortnight of the Academy which will be held from November one to twelve is, The Medical and Surgical Disorders of the Urinary Tract. The program gives promise of providing a valuable and interesting symposium. Fortunately the subject embraces medicine and surgery and many allied special fields. The Committee has made every effort to provide an integrated program with topics of present interest, which will be discussed by men particularly qualified to present the subject with authority and clarity. The Committee has also arranged morning and afternoon clinics in leading hospitals of New York City which have, as in past years, generously cooperated in the plans for this year's program. Insofar as possible the hospital clinics each day will be devoted to the topics of the evening program of the same day. The rich store of clinical material available in this city will thus be demonstrated by distinguished clinical teachers, including such leading men from other medical centers of this Country as may be invited jointly by the participating hospitals and the Academy.

The subject of this year's Fortnight is unusually suitable for Exhibits. The Committee therefore plans to exploit this opportunity fully, particularly with a view to having special demonstrations of exhibits on two afternoons of each week.

In general terms the first week of the Fortnight will be devoted to medical and the second week to surgical subjects. The program of the evening meetings follows:

Physiology of the kidney ..... Alfred N. Richards
Tests for kidney function ..... Donald D. Van Slyke
Edema and its treatment ..... Dana Atchley
Uremia and pathology of kidney function ..... Arthur M. Fishberg
Pathology of vascular disease ..... Milton C. Winternitz
The pathology of nephritis ..... George Baehr
Clinical aspects of nephritis ..... Robert F. Loeb
Nature of hypertension ..... Irvine H. Page
Clinical aspects of hypertension, including malignant hypertension ..... Herman O. Mosenthal
Evaluation of the surgical treatment of hypertension ..... George J. Heuer
The nephroses ..... Albert A. Epstein
Vascular and renal complications of pregnancy ..... W. W. Herrick
The psychological factor in hypertension ..... Karl A. Menninger
Pathogenesis and treatment of renal infections ..... William F. Braasch
Renal and perirenal infections ..... Hugh Cabot
Renal tuberculosis ..... John R. Caulk
Calculus disease. The formation of stones ..... Linwood D. Keyser
Clinical aspects of calculus disease ..... Henry G. Bugbee
Hydronephrosis and pyonephrosis ..... J. Bentley Squier
Bright's disease in children ..... John D. Lyttle
Common urologic diseases in children ..... Meredith F. Campbell
Radiotherapy of tumors of the urinary tract ..... Benjamin S. Barringer
Tumors of the kidney and ureter ..... Archie L. Dean, Jr.
Tumors of the urinary bladder ..... Edwin Beer
Pathologic physiology of bladder neck obstructions ..... William E. Lower
Transurethral resection of bladder neck obstructions ..... Joseph F. McCarthy
Surgical treatment of obstructions at the neck of the bladder ..... Hugh H. Young

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PHOTO I
Rachitogenic Diet No calcium deposit
PHOTO II
Rachitogenic Diet with 4 and 7% VEGEX
PHOTO III
Rachitogenic Diet with 1/3 Dried Whole Milk

No. 1 No. 2 No. 3

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